DRUGS from PLANTS

SIGMA INTRODUCTIONS TO SCIENCE

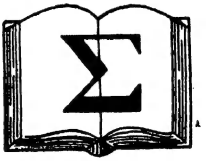
1. FRONTIERS OF ASTRONOMY by David S. Evans, M.A., Ph.D., F.Inst.P.
2. SCIENCE VERSUS CANCER by I. Berenblum, M.D., M.Sc.
3. WHAT IS ATOMIC ENERGY? by K. Mendelssohn, M.A., Ph.D., F.Inst.P.
4. ELECTRONS IN ACTION by J. G. Daunt, D.Ph., M.A.
5. POWER by M. Ruhemann, D.Phil.
6. MOLECULES AGAINST MICROBES by E. S. Duthie, M.B., Ph.D.

All the above volumes are fully illustrated and uniform with this book.
6s. net

DRUGS from PLANTS

Trevor Illtyd Williams
B.A., B.Sc., D.Phil.
Deputy Editor of *Endeavour*

'O mickle is the powerful grace that lies
In herbs, plants, stones, and their true qualities"
Romeo and Juliet, II, iii.



SIGMA

Sigma Introduction to Science 10

CONTENTS

LIST OF ILLUSTRATIONS

Plate X. The Purple Foxglove. *Digitalis purpurea.* (From Nicolaus Bassaeus *Eicones Plantarum.* Frankfort, 1590.)

Plate XI. (*Right*) Part of the laboratory plant used by the Oxford team of penicillin research workers.
(*Left*) Purification of penicillin by chromatographic analysis—*see* page 70.
(*Bottom*) A plant used to prepare penicillin on a commercial scale. (Imperial Chemical Industries' photograph.)

Plate XII. An Arab Pharmacy of about the 10th century which was discovered in almost original condition and reconstructed in the Wellcome Historical Medical Museum.

The pages containing the illustrations will be found following Page 40.

CHAPTER ONE

INTRODUCTION

FROM the earliest times the sciences of medicine and botany have been very closely linked. Recognition of the medicinal value of certain plants seems to have occurred very early in the history of all known peoples; certainly it was a discovery which long preceded the art of writing. One of the earliest references to the medicinal use of plants is found in the Ebers Papyrus, which was discovered in 1873; this dates from approximately the 16th century B.C. It describes more than 700 herbal remedies, including many which are familiar today, for the list mentions poppy, castor-oil, squills, aloes, and caraway. Old though this manuscript is, its general style and the numerous marginal notes indicate that it forms a summary of medical lore which was already old at the time of writing. It can, therefore, be said that the use of plants for treating disease dates back for at least four thousand years. Although modern scientific developments have greatly changed the methods of medicine and introduced new drugs which are unknown in nature, drugs derived from plants still find extensive, and indeed increasing, use. Penicillin, one of the newest and most valuable of all drugs, is of vegetable origin.

Ancient science, and especially the science of medicine, is closely wrapped in mysticism. While the physicians, or their primitive equivalents, sought on the one hand for effective remedies for the many diseases which afflicted their peoples, on the other hand they sought to cover their ignorance and mistakes by combining their treatment with elaborate ritual. This tendency resulted also from their failure to understand the causes of disease. So long as evil spirits were regarded as a major cause the appeal to spiritual rather than material remedies was a natural one. In almost all early writings, therefore, the remedies, even those which we recognise today as being effective, were accompanied by the chanting of spells, the wearing of amulets, and similar superstitious practices. When a cure resulted the spells were as likely to receive the

credit as the medicine, but as the physician was the source of both, his skill would in either case be applauded. When treatment failed he had at least the excuse that no man could be expected to be familiar with all the changing moods of evil spirits.

To the early Egyptians such a mystical system of medicine must have come very naturally. The multiplicity of their gods and their attendant spirits encouraged a belief in evil spirits as a source of sickness. Their views on the life after death led them to develop the art of embalming to a very high degree. In acquiring this art they not only learnt the properties of many herbs, which they used also to heal the living, but acquired also a knowledge of human anatomy. The Ebers manuscript mentioned above shows that their knowledge of medicinal herbs was considerable even by the 16th century B.C. Examination of human remains of similar antiquity shows that their surgical skill was also great.

Many of the medicinal herbs of the Egyptians seem to have been chosen primarily for their aromatic properties. Pleasant smells were believed to ward off the evil vapours of disease—no doubt they were also favoured because of their power of overcoming the disagreeable smells which accompany many diseases. It may be mentioned that this reliance on aromatic substances persisted throughout the history of medicine. In mediæval times physicians carried a nosegay of sweet-smelling flowers. Contemporary prints sometimes show them wearing an elaborate cowl designed so that the air they breathed could first be drawn through a pad of herbs. The gold-headed cane, which was traditional for doctors almost up to the present time, is said to be symbolic of the pomander of their predecessors. Apart from their aromatic herbs, however, the Egyptians were undoubtedly familiar with several which have real therapeutic value. The soporific effects of poppy preparations were evidently known to them ; it is doubtful, however, whether they made use of its pain-killing properties in their surgical operations. Aloes and castor-oil were familiar to them as purges. Squill, or the sea onion, which grows extensively on the borders of the Mediterranean, was also known to them, but the use they made of it is obscure. To-day squill is known to contain a drug, similar to digitalis, the active

principle of fox-glove, which has a powerful effect on the rhythm of the heart. The following is a typical recipe from the Ebers papyrus :

> To keep the hair from falling out. Mix together artists' colour, collyrium, *khet* plants, oil, gazelle dung and hippopotamus fat and rub the mixture on the head.

For a purge the following is recommended :

> Field herbs $\frac{1}{8}$, honey $\frac{1}{8}$, dates $\frac{1}{8}$, *uah* grain ; mix together and chew for one day.

Egyptian medicine decayed along with the kingdom of Egypt itself, but elsewhere a new school of medical thought was growing up. Babylon, famous for its material glories, is equally memorable for its intellectual achievements. Babylonian medicine can be traced back as far as 2000 B.C. and its antiquity is thus as great as that of Egypt. It was at its height, however, very much later—about 700 B.C. The so-called Code of Hammurabi, the oldest written legal code of which we know, contains several laws relating specifically to the practice of medicine. Their wording makes it clear that a high degree of skill had been reached, particularly in surgery, for precise penalties were prescribed for unsatisfactory outcomes of quite elaborate operations. It is interesting to note that the penalties were graded according to the social status of the patient. Medicine must have been a hazardous occupation, for a doctor might pay with his life for the fatal outcome of an operation on a member of the upper classes ; for the death of a slave, however, he could compound for a few pieces of silver. As in Egypt, medicine had a strong admixture of magic. An effective remedy was generally combined with an incantation as an additional safeguard. Tooth-ache, for example, was believed to be caused by a worm. Treatment was by means of a mixture of henbane and resin—no doubt effective enough, for this plant contains substances which deaden pain. It was recommended, however, that at the same time the patient should call down the wrath of the god Ea on the worm causing the pain. It is of interest that this belief in a worm as the cause of tooth-ache is held to-day by the peasants of Eastern Europe ; possibly there is an unbroken tradition. The Assyrians made use of about 250 vegetable drugs, including asafoetida, saffron, cardamom, mandrake, poppy, and lupin.

Modern medicine is generally considered to date from the time of Hippocrates (460–361 B.C.). He was, however, himself the grandson of another famous physician, Nebrus, and the heir to an already well-established school of medical thought. His great contribution was to sweep away a great deal of the mystical element, though much of it crept back later, and introduce the precision which had previously been lacking in his profession. It was he who first firmly established the principles of diagnosis and prognosis. He stressed the importance of careful observation of the symptoms of the individual patient, and it was on this, rather than on the haphazard methods of his predecessors, that he based his methods of treatment. Such records of his cases as have survived read very much like the case-notes of a modern doctor. From the writings attributed to him it appears that he made use of three or four hundred different drugs, the majority of them of vegetable origin. The teaching of Hippocrates, though sometimes lost sight of and ignored for long periods, has had a profound influence on the development of medicine and one which is apparent even today. For the first time medicine became a science as well as an art. Not for five centuries was a figure of comparable importance to arise. Galen (103–193 A.D.) was a Roman physician who carried on, though introducing his own ideas, the teaching of Hippocrates. Born at Pergamus, the son of an architect, he was early attracted to the study of philosophy, mathematics, and medicine. After visiting Greece and Egypt, countries with long medical traditions, he settled in Rome and soon proved so successful that he came under the patronage of Marcus Aurelius. He wrote widely, some three hundred volumes being attributed to him, but unfortunately the greater number of these were destroyed by fire in the Temple of Peace at Rome. The cry "Physician heal thyself" is often heard. It is, therefore, interesting that both these great figures of early medicine lived to a ripe old age, Hippocrates to 99 and Galen to 89.

Hippocrates and Galen together dominated European medicine for some fifteen centuries, though in the absence of original thinkers and experimenters their teaching was allowed to turn into dogma and, with the passing of time, became distorted and misunderstood. Their interest was in medicine

as a whole rather than in one particular part of it. Diocles Carystius compiled the first Greek herbal in the fourth century B.C., but no copy of this is now known. Theophrastus (372–285 B.C.) included in his writing the *Historia Plantarum* which listed 500 plants ; it is possible, however, that this list was originally compiled by Aristotle (384–322 B.C.). For one of the first important specialists in the study of plants and drugs we must turn to Crateuas, of the first century B.C., who was private herbalist to Mithridates VII, King of Pontus. He is noteworthy less for the value of his own medical work than for his production of the first extant illustrated book on medicinal plants. Somewhat later, in the first century A.D., Dioscorides, a Cilician, who is said to have been personal physician to Nero, founded the study of *materia medica*, i.e. the materials of medicine. He wrote a book on medicinal herbs in which was described some six hundred plant products, with an indication of the diseases for which they were to be used. Both Crateuas and Dioscorides had a great influence on the herbalists of later centuries.

Another great and influential figure of the first century A.D. was the elder Pliny. He was not a physician, but what we should now call a natural philosopher. A man of great intellectual capacity and industry, the whole field of nature became his subject. No phenomenon was too small for his attention, none too great. It was indeed his curiosity that brought about his death, for he was killed while attempting to observe an eruption of Vesuvius. Of his many books none are now extant except his Natural History, a vast work in thirty-seven volumes. It is, in fact, an encyclopædia of all the physical knowledge of the time. To a considerable extent this book is a summary of the opinions of his contemporaries and predecessors rather than an account of his own observations. To modern minds at any rate he seems to have been very credulous, for he includes detailed accounts of such freaks as mermaids, one-footed men who sheltered from the sun under their one enormous foot, winged horses, and headless men whose features were on their chests. Unfortunately he knew little of medicine, but in spite of this his reputation in other respects was so great that, as with the other subjects on which he wrote, his opinions were widely accepted for many centuries.

In dealing with medicinal plants he put forward the theory that for every disease there was an appropriate herbal remedy if only this could be found. Unfortunately he suggested no methods for identifying the proper plants, but it is possible that from this suggestion the so-called Doctrine of Signatures ultimately evolved.

This ill-founded doctrine, which so greatly occupied the minds of physicians for many centuries, led to the development of herbal treatment along almost completely erroneous lines. Because Pliny had said that every disease had an appropriate herbal remedy, philosophers, with little or no experimental work to back them, put forward the theory that every plant carried somewhere on it a mark or symbol to indicate the medical purpose for which it was to be used. Had this been true medical practice would have been greatly simplified ; unfortunately, it was not true and the result was hopeless confusion. Although this was an utterly false theory its influence on the development of medicine, and in particular on the use of medicinal plants, has been so great that it deserves more than passing mention.

The names of many common herbs have originated in the Doctrine of Signatures. Thus Solomon's Seal owes its name to the fact that if the root is cut across the section resembles a seal. Hence it was supposed that preparations of the plant would be valuable for sealing wounds, and it was widely used for this purpose. One old writer charmingly expresses this by saying that it is helpful for relieving the injuries caused" by women's wilfulness in stumbling upon their hasty husbands' fists." The mandrake root, from its frequent resemblance to the human body as a whole, came to be regarded as an almost universal cure for bodily ills, and much superstition surrounded it. The vendors of the root fostered the story that when it was pulled out of the ground it emitted a piercing shriek, immediately fatal to all who heard it. As such a story immediately suggested, at any rate to the less credulous, that the seller had no right to be there in person to tell the story, the method of gathering the root was said to be as follows. A dog was tied to the head of the root by a string. The herb-gatherer then stopped his ears with wax and, after retiring to a safe distance, whistled to the dog. In answering the call the dog

pulled the root from the ground, though it was killed by the shriek of the mandrake in doing so. This fabrication had the additional advantage that the obviously high mortality among dogs justified the high price asked for the root. Plants with yellow flowers, or those which exuded a yellow juice on pressing, were recommended for jaundice. Herb-Robert (a variety of Crane's-bill) was used for treating hæmorrhage on no other grounds than that it assumed a red tint when dying. Saxifrage (stone-breaker) owes its name to its habit of growing in the crevices of stones. Because of this habit it was believed to be valuable for breaking up "stones" in the kidney—certainly more a play upon words than upon reason. Liverwort, a plant whose three-lobed leaves have some resemblance to the liver, was duly prescribed for disorders believed to arise from that organ.

Although this theory was entirely without foundation it did at least cause the old herbalists to examine carefully all the plants they could, if only to look for the imaginary symbol which would indicate its use. In this way they acquired a great store of botanical and medical knowledge, just as the alchemist, in his vain search for the Philosopher's Stone, laid the foundations of modern chemistry.

Herbalism flourished also among the Arabs. From the fifth century onwards Greek and Roman works on the medicinal properties of plants were translated into Arabic. The great Arabic physicians Rhazes (866–925 A.D.) and Avicenna (980–1036 A.D.) made extensive use of herbs. Perhaps the greatest of Arabic herbalists, however, was Abd-Allah ibn Al-Baitar, who died in 1248. Born at Malaga he travelled extensively in Greece, Egypt, and Asia Minor. At Cairo he composed the great *Arabic Herbal.* This contains the names of more than 800 plants ; although based on the work of Theophrastus, Dioscorides, and Galen, it contains additions and corrections of his own.

One of the greatest stimuli to medicine and herbalism, as to all other branches of learning, was the invention of the process of printing by movable type. As a result books, hitherto available only in the form of laboriously prepared copies of the original manuscript, became available in relatively large numbers at a reasonable price. Printing was probably

first practised in 1450, by John Gutenburg at Mainz. In England the first press was set up by Caxton in London in 1476. By the year 1480 nearly two hundred editions of medical books had been printed ; six of them were reprints of Greek and Roman classics, including the works of Hippocrates, Pliny, and Galen.

Soon many of the older herbals found their way directly into print, or provided material for newer and more extensive works, and the literature of herbalism reached large proportions. One of the earliest known manuscripts on herbs is that of Macer : this is a Latin poem, probably of the tenth century, describing the virtues of nearly eighty plants. The Leech Book of Bald is another work of the same period, though probably to a large extent a copy of much earlier manuscripts, being more a collection of the herb lore of the time than an account of original work. One volume of the vast *De Proprietatibus Rerum* of Bartolomaeus Angelicus is devoted to a description of medicinal herbs. The manuscript version dates from about 1250. It was translated into English in 1398 and first printed, at Basle, in 1470.

By the sixteenth century the art of herbalism had become firmly established. The herbal remedies of many people and many centuries had been recorded in fairly readily accessible form, though the grain was still scarcely separated from the chaff, and the time was ripe for herbalism to become an effective weapon for fighting disease. Paracelsus (1493–1541) had, in his extensive writings, begun to bridge the gap between medicine and chemistry and thus founded *iatrochemistry*. His successors, van Helmont (1577–1644) and Franciscus Sylvius (1614–1672) were to continue his work ; their attempts to interpret physiological processes in chemical terms led logically to the use of chemicals in an attempt to restore the balance when these processes went wrong in disease. Gardens devoted exclusively to the growing of medicinal herbs were established in various parts of the country. John Gerarde, for example, author of a famous herbal, cultivated an extensive herb garden at Holborn. A catalogue published in 1596 lists over 1,000 different plants. His *Herball* was issued in the following year and in it he describes :

> " not only the names of sundry plants but also their natures, their proportions and properties, their affects and effects, their increase and decrease, their flourishing and fading, their distinct varieties and severall qualities, as well as those which my own Countrey yieldeth, as of others which I have fetched further."

Gerarde's *Herball* is not an original work, but is based on Dodoens' *Stirpium Historiae Pemptades Sex* of 1583. It is a curious book, a mixture of accurate description and contemporary folk-lore. Much of the latter must have seemed very dubious even to the readers of his own time. He tells, for example, of a tree which produced geese as living fruit ; this is a story as fantastic as some of those told by Pliny some fifteen hundred years before. In spite of its defects and plagiarism, however, the book gives an excellent account of the state of herbal knowledge at the end of the sixteenth century.

Many of the methods of the herbalists of this period are similar to those used in pharmacy to-day. Thus William Coles writing of Selfe-Heal (*Prunella vulgaris*), a much-esteemed plant writes :

> " There is not a better Wound-herbe in the world than that of Selfe-heal is . . . being only bruised and wrought with the point of a knife upon a Trencher or the like, will be brought into the forme of a Salve, which will heal any green (gangrenous) Wound, even in the first intention."

This is similar to the modern method of grinding herbs in a mortar and then extracting with water or other suitable solvent. Askham's edition of a famous herbal by Banckes, the latter first published in 1525, gives another excellent example of the herbal practice of the time. One recipe given by Askham (1550) reads :

> " Go to the roote of woodbinde and make a hole in the middes of the roote, then cover it well againe that no ayre go out nor that no rayne go in . . . let it stand so a night and a day . . . and thou shalt fynde therein a certain lycoure. Take out that lycoure with a spone and put it into a clean glas and do so every day as long as thou

> fyndest ought in the hole, and this must be done in the moneth of April or Maye, then anoynt the sore therewith against the fire, tha wete a lynnen clothe in the same lycoure and lappe it about the sore and it shall be hole in shorte space on warrantyse by the Grace of God."

As might be expected from the circumstances of their origin many of these remedies were valueless, but mixed with them are many which have stood the test of time and, in a suitably modified form, are in use to-day. Quinine, for example, in the form of an extract of " Peruvian Bark," was in use as early as 1630 (see Chapter IV). In the sixteenth century the Bavarian doctor, Fuchs, showed that a preparation of the common fox-glove is valuable in the treatment of certain kinds of dropsy. This remedy, too, is widely used to-day (Chapter VI). The sixteenth and seventeenth centuries mark the transition between the old mediæval herbalism, with its burden of superstition, and the modern use of herbs, based on careful observation and controlled experiment. Nevertheless the older methods died hard and, as a curious anachronism, even persist at the present time. Fantastic remedies were no monopoly of the Middle Ages. Just as they are today, the common people were readily led astray by rogues who hid their ignorance in a spate of herbalist jargon. As late as 1739, and possibly a good deal later, Venice Treacle enjoyed considerable popularity. This famous remedy, said to have been devised by Dioscorides himself, was evidently compounded in the belief that the more ingredients you put into a remedy the better it must be. A version of 1651 was as follows :

> " vipers, white wine, opium, ' spices from both the Indies,' liquorice, red roses, tops of germander, juice of rough aloes, seeds of treacle mustard, tops of St. John's wort, and some twenty other herbs to be mixed with honey . . . into an electuary."

In 1739, too, even so learned a body as the British Parliament was taken in by a plausible quack. A woman named Joanna Stephens announced that she had a remarkable and unfailing cure for stone. This she offered for sale for the sum of £5,000. In a short time £1,356 was raised by subscription but, further funds proving difficult to obtain, the matter was

then raised in Parliament. A learned commission, which included the Archbishop of Canterbury, several bishops, peers, and doctors, was appointed to investigate the remedy. So impressed were they that they stated that they were " convinced by experiment of the utility, efficacy and dissolving power " of the remedy. Joanna Stephens received her fee and the supposed remedy was published. She stated :

> " My medicines are a Powder, a Decoction and Pills. The Powder consists of egg-shells and snails, both calcined. The Decoction is made by boiling some herbs (together with a ball which consists of soap swine's-cresses burnt to a blackness, and honey) in water. The Pills consist of snails calcined, wild carrot seeds, burdock seeds, asken keys, hips and hawes, all burnt to a blackness—soap and honey."

Even within living memory remedies just as fantastic were accepted in the more remote parts of our own country. The following report is taken from the *Pall Mall Gazette* of October 12th, 1866, describing the account given at an inquest on a child of five who had died from hydrophobia :

> " Sarah Mackness stated that at the request of the mother of the deceased she had fished out of the river the body of the dog by which the child had been bitten, and had extracted its liver, a slice of which she had frizzled before the fire, and had then given it to the child to be eaten with some bread. The child ate the liver greedily, drank some tea afterwards but died, in spite of this strange specific."

The phrase " in spite of " seems hardly appropriate.

Even today worthless herbal remedies enjoy a considerable vogue among the superstitious and uninformed, but as we shall see in the next chapter, herbalism and medicine have been united by the application of modern scientific methods, to the advancement of both arts and the benefit of mankind.

CHAPTER TWO

SCIENCE AND THE ART OF HERBALISM

BY the end of the seventeenth century most of the herbal lore of the previous three thousand years had been permanently recorded in book form. A vast amount of empirical knowledge had been accumulated and for further progress to be made it became necessary to sort out the comparatively few really effective remedies from the great bulk which had their origin in ignorance and superstition and had nothing but tradition to recommend them. To bring order out of chaos the herbalists had to look to the future instead of to the past ; it was no longer sufficient " to read Dioscorides, to know the nature of plants and herbes " (William Bullein, the " Government of Health," 1558).

Progress came with a return to the scientific method, based on observation and experiment, recommended to physicians by Hippocrates more than two thousand years previously. By carefully observing the effects of various drugs on the course of disease it was gradually possible to sort out many of those preparations which were genuinely beneficial. A number of these, as we have already seen, were remarkable for the complexity of their composition. Many of the ingredients were added more in the belief that they would do no harm than with evidence that they would do good. Nevertheless, because they included some drugs of real value, a number of these elaborate formulæ were effective. Thus William Withering is said to have discovered the medicinal value of foxgloves by investigating an old country remedy for dropsy which contained more than twenty other herbs. Gradually useful plants were distinguished from those to which, even today, no decisive therapeutic value can be attached.

At the same time chemistry, in a rather similar way, was being built as an exact science on the basis of the knowledge gained by the alchemists in their vain search for the Philosopher's Stone and a means of transmuting base metals into gold. By the eighteenth century the sciences of chemistry and

pharmacy, long contiguous, were overlapping to a considerable extent. The pharmacists were investigating the medicinal properties of the new products made available by the chemists. The latter, for their part, were investigating the chemical nature of the drugs used by the pharmacists. This interlocking of the two sciences had a great influence on the development of both. To a considerable extent the pharmacists had been able to separate the useful plants from the useless ; with the help of the chemists it became possible for them to reject in addition the inactive parts of plants they knew to be of medicinal value. Before the end of the eighteenth century, for example, Fourcroy had been able to extract crude crystalline quinine from cinchona bark. This process of extracting the active principles of natural drugs was greatly extended during the nineteenth century and today is a most important branch of science.

The use of medicinal plants in their natural state presents several difficulties. Their actual content of the active drug varies with both the locality and the season in which they are gathered. Many of the ancient herbalists were evidently well aware of this fact for they frequently specified the drugs of a particular region as possessing the greatest medicinal virtue. Often, too, they directed that the herbs should be gathered at a particular season of the year or phase of the moon. It must not be presumed, however, that all their directions of this kind arose from real knowledge ; doubtless they were often given merely to impress the uninitiated or as a relic of old magical rites. As the active principles of many plants are powerful poisons when taken in excess, the dangers of prescribing drugs of uncertain origin are obvious. Equally the patient may suffer if the drug is of lower activity than usual, for in that case an under-dose may be given and the expected relief not be obtained. Many drugs, too, deteriorate on storage. Foxglove leaves, for example, quickly lose their medicinal properties unless dried very soon after gathering ; in the damp leaves the active substances rapidly decompose. Yet another argument against the use of raw drugs is that many contain, besides the substances to which the medicinal value is due, other substances which have only harmful effects. In the case of penicillin, for example, it has been found that the crudest

preparations are unsatisfactory because they contain pyrogens, substances which cause fever.

In modern pharmacy these difficulties are overcome by two main methods. One is to standardize drugs by means of biological tests. Thus penicillin preparations (Chapter VII) are assayed by observing their effect on the growth of a common type of bacteria, generally *Staphylococcus aureus*, the common organism of infected wounds. Hashish, the hemp drug (Chapter V), can be assayed by observing the quantity necessary to produce ataxia (lack of muscular control) in dogs. Substitutes for quinine are tested by observing their effects on the course of malaria induced in birds, generally canaries or chicks. Many tests of this kind are prescribed in the various pharmacopœias. The latter are books which define the standards to which the articles of Materia Medica (page 13) must by law conform. Most countries have their own pharmacopœias, though the prescribed tests generally show comparatively little variation from one country to another. Biological tests are in the main satisfactory but have the disadvantage that they are rarely capable of high accuracy, are almost always time-consuming, often require numbers of experimental animals, and generally can be carried out only in a well-equipped laboratory.

Medicinal plants owe their therapeutic properties to the presence in them of one or more definite chemical constituents. All plants contain a great number of inactive substances such as water, cellulose, lignin, glucose, and starch. It is true that some of these have nutritive value but all ordinary diets contain them in abundance. As mentioned above, toxic substances, too, are often present. It is, therefore, logical to try to isolate the substances possessing medicinal properties and to discard the remainder of the plant. In a great many cases this aim has been achieved. Quinine, in the form of pure white crystals, can be isolated from cinchona bark and huge quantities are sold in this form ; crystalline penicillin has been isolated from the crude liquid in which the mould *Penicillium notatum* has grown ; large quantities of strychnine are isolated every year from the seeds of *Strychnos nux vomica*. Several great advantages result from the use of pure drugs instead of the crude plant. One of the greatest is that when a dose is

prescribed it can be measured by weight. A pair of scales, or a balance as the chemist generally calls it, is both simple to use and capable of high accuracy. If a doctor in, let us say, Sydney, finds that ten grains daily of a certain drug will relieve some condition of disease, then any doctor in the world who has access to the pure drug and a simple balance can at once begin similar treatment for his own patients. Another great advantage, which will be further discussed in a later chapter, is that by chemical investigation it may be possible to find out the exact composition of the natural drug and to synthesize it economically and thus avoid altogether dependence on plants. Furthermore, by varying slightly the composition of the drug, it may be possible to improve on nature or to increase the scope of the natural product. For example, cocaine, the active principle of coca leaves (page 99) is a most valuable local anæsthetic but has the disadvantage of being rather poisonous. By chemical investigation it was possible to determine the constitution of cocaine and then to prepare it in the laboratory. By modifications of the original preparative method a whole range of new drugs related to cocaine has been obtained. Though many of these proved unsatisfactory, a number, such as stovaine and holocaine, have been introduced into general medical practice. A particularly valuable derivative is novocaine, whose toxicity is only a fraction of that of cocaine.

Many hundreds of drugs have already been isolated from plants in the pure state and a considerable number of them are prescribed in the pharmacopœias of the world. Not in all cases, however, has it proved possible to isolate the pure principle of plant drugs. In these, however, it is frequently possible to effect a great concentration of the active principle by chemical methods and to obtain a preparation which is not only far more active than the raw material but also possesses very much better keeping qualities.

The systematic chemical investigation of plants has revealed the existence of a number of new drugs which, because of the very small traces in which they normally occur, would have passed unnoticed if the crude material alone had been used. An excellent example of the value of such research is provided by work recently carried out at Oxford and later

independently, in the United States. The old herbalists had many salves for the treatment of " green wounds," i.e. infected wounds. In view of the claims made for these salves it was thought possible that some of the plants used might contain antibacterial substances. Accordingly extracts of some 3,000 different plants were prepared by methods similar to those of the old herbalists and were tested against cultures of simple infective bacteria such as *Staphylococcus aureus* and *B. coli.* Results were very encouraging. The extracts of some thirty different families of plants were found to contain substances which inhibited the growth of bacteria. It was evident, however, that many of these substances, when used at concentrations high enough to kill bacteria, were too toxic and irritating to be used medicinally. A number of pure antibacterial substances have been isolated from the plant extracts and an investigation of the therapeutic possibilities of these is now being made. It is interesting that many of the plants most prized by the herbalists produced negative results when tested. Self-heal (*Prunella vulgaris*), for example, of which William Coles wrote " There is not a better Wound-herbe in the world than that of Selfe-heale," failed to show any antibacterial activity under the conditions of the experiments. (Plate II).

It has been seen that valuable as some of the old herbal remedies were, the weight of superstition, error, and ignorance retarded progress until scientific methods were introduced to separate the grain from the chaff. The modern science of pharmacology owes much to the work of the old empirical herbalists and this debt must not be underestimated. Nevertheless modern pharmacy is so far ahead of the herbalism of a century or two ago that it is astonishing that the older form of the art should have survived up to the present time. Herbalists' shops still exist in all parts of Great Britain and throughout the world. Indeed the advent of commercialism has made herbalists' shops perhaps more numerous than they have ever been. They enjoy a considerable and profitable trade, primarily from those who are ignorant of developments in orthodox medicine and who like a dash of mysticism thrown in with their treatments. A recent Act of Parliament, restricting the powers of the herbalists, has aroused public interest in their activities and it is, therefore, timely to discuss, from a

scientific point of view, the present relationship between herbalism and medicine.

An essential feature of modern scientific method is the controlled experiment. When we deal with very complicated problems, such as the treatment of disease, it is essential, if trustworthy results are to be obtained, to find a method of eliminating disturbing effects which cannot easily be allowed for. The course of a disease is not affected only by the drugs given to the patient; innumerable other factors, such as climate, temperament, nutrition, and general state of health, play a very important part. To get a true estimate of the value of any drug it is necessary to compare the reaction of patients receiving the drug with a similar number, whose treatment is in every other way identical, who receive no drug. By using the untreated series as a " control " the effects due to the drug itself can be distinguished from those due to other causes. Such controls are, for humanitarian and other reasons, not always easy to apply to human subjects but experiments of this kind can legitimately be carried out with animals and much useful pharmacological information has been gained from them. The value of penicillin, for example, was first demonstrated by infecting mice with a lethal dose of bacteria (staphylococci) and treating half of them with penicillin, the other half forming a control. Nearly all the controls died; nearly all the treated mice recovered. Even under such rigid experimental conditions, however, mistakes can arise from unexpected complications. A year or two ago, for example, it was claimed that a mould product, patulin, was an effective cure for the common cold. The original publications were not unconvincing but further research showed that the claims made for patulin could not be substantiated. The herbalists made use of no such refined methods. In general it was accepted that if recovery followed the use of a particular drug, then the latter had played some part at least in bringing about this result. In a number of cases, as we know, this kind of reasoning led to the right result; in many others it proved quite wrong. Under rigid tests by modern methods many herbalist remedies have quite failed to justify the claims made for them. This is not surprising when we remember that many of them were based on completely false premises, such as the Doctrine of Signatures.

Modern herbalists accept much that is unproved and have failed to appreciate, or at least to accept, the great benefits that the use of scientific methods can confer on their art. Arguments have already been advanced (page 21) against the use of unrefined plant products, and reasons given for preferring to use pure substances, either isolated from plants or prepared synthetically. Against this some herbalists have argued in a way that does little credit to their own powers of reasoning or to the intelligence they ascribe to their audience. Briefly, they claim that herbal remedies are of particular merit because they are "natural." They seem to think that in the process of isolation substances undergo mysterious changes which cause them to lack the virtue which they possess in the raw material. Such an argument is untenable because it is completely at variance with the facts. Pure crystalline penicillin is exactly as effective against bacteria as an equivalent quantity of the crude material. Scurvy is as readily cured by pure synthetic vitamin C, which never saw a plant, as it is by natural sources of the vitamin. Synthetic quinine cures malaria as effectively as crude extracts of cinchona bark.

There is a further important argument against the continuance of herbalism, as such, in the treatment of disease. Too often it is argued that if herbalists do little good, they are essentially harmless. Against this it must be remembered that the efficiency of any treatment depends on accuracy of diagnosis. The ordinary herbalist does not have the training necessary to diagnose any but the most obvious ailments; his powers in this respect rarely exceed those of the average, intelligent citizen. Even if one allowed that his remedies are as effective as he claims, his severe limitations in diagnosis inevitably detract from the value of the treatment he prescribes. This is a most serious matter. For minor ailments incorrect diagnosis and treatment may cause the unlucky patient nothing more than inconvenience; if the disease is serious delay in seeking properly skilled assistance may even prove fatal.

Medicine has greatly benefited from the empirical discoveries of the herbalists; undoubtedly many discoveries remain to be made. Herbalism in a new guise—the investiga-

tion of plant products in properly equipped laboratories, by trained research workers—has a great future. So far as medicine is concerned the day of the older kind of herbalism is over, and the sooner this fact is recognized the better. It must not be forgotten, however, that the modern herbalist shops serve a useful purpose in supplying herbs for purposes other than medicinal ones. Many plant products, such as caraway seed, mint, thyme, and cardamon seed, are much valued for culinary purposes. Others, such as lavender, are prized for their aromatic qualities. Tobacco is a herb which comparatively few do not use ; herbalists commonly stock curiously compounded herbal smoking mixtures. In supplying wants such as these the herbalists can still serve the public well.

CHAPTER THREE

THE KINDS OF DRUGS OBTAINED FROM PLANTS

THE ordinary citizen uses the word drug for any substance, or mixture of substances, which is used medicinally, but generally does not appreciate how many different kinds of drug there are or the variety of purposes to which they can be put. One important function of science is classification, and although any detailed scheme is inappropriate to a book such as this, a brief account of the way in which drugs can be classified will help to clarify the accounts of individual drugs given in later chapters.

One method of classifying drugs is by relating them to the species of plants from which they are obtained. Thus a large group of drugs can be defined as the opium drugs, because they occur in opium, the solid obtained by drying the juices expelled from the seed vessels of a species of poppy, *Papaver somniferum*. The opium drugs include such substances as morphine and codeine, as well as narcotine, laudanine, and a variety of others. The cinchona drugs are derived from cinchona bark. Besides quinine, this group includes cinchonine, cinchonidine and quinidine. The so-called Nux Vomica drugs are those obtained from the seeds of *Strychnos nux vomica*; they include strychnine and brucine. A botanical classification of this sort has the advantage that all drugs derived from a single source are brought under one heading, but it has the disadvantage that it brings together many drugs which differ widely in both their physiological and chemical properties. For many purposes it is more satisfactory to classify drugs on a chemical basis, but before such a classification can be explained a little must be said about chemical formulæ.

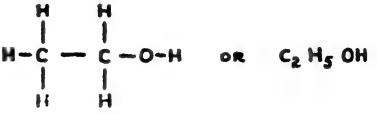
Most people are familiar with the fact that all matter is composed of minute, ultimate particles which we call atoms. There is good evidence, with which we need not concern ourselves here, that all matter is made up from only ninety-two different kinds of atoms, the atoms of the elements.

Water, for example, consists of molecules (compound atoms) each consisting of two atoms of hydrogen combined with one atom of oxygen. By various methods, such as the passage of an electric current, these molecules can be broken up again, giving gaseous hydrogen and oxygen. We need not be surprised that the properties of water differ so greatly from those of either of its two constituents. For example, the properties and uses of a nut and a bolt together differ widely from those of either taken separately. To take a more elaborate example, the nature of a motor-car bears scarcely any resemblance to that of its numerous component parts. In the chemistry of drugs five elements are of particular importance—carbon, nitrogen, hydrogen, oxygen, and sulphur. Carbon differs from all other elements in the variety and complexity of the combinations into which it can enter. While most atoms can combine only in twos and threes, carbon atoms can combine in tens, hundreds, or even thousands. In view of this it is not surprising that the chemistry of living matter is essentially the chemistry of compounds of carbon. Almost all drugs derived from plants are combinations, of one kind or another, of the five elements listed above. At first sight it may seem remarkable that substances differing so widely as, say, penicillin and strychnine, could both be formed of such a limited number of unit parts. Yet it must be remembered that from a small range of materials, such as bricks, mortar, planks, slates, and girders, the builder can make buildings as diverse in their appearance and purpose as churches and public-houses, bungalows and mansions, skyscrapers and dog-kennels. By various methods it has been possible to find out exactly how the individual atoms are arranged in a wide variety—hundreds of thousands—of different substances. Every individual substance has its own special arrangement of atoms which distinguishes its molecules from those of all other substances. For convenience the chemist uses a special shorthand method for describing the arrangement of atoms in any given kind of molecule. The atoms of each element are represented by single (sometimes a pair of) letters, e.g. :

Carbon = C Nitrogen = N

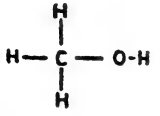
Hydrogen = H Oxygen = O Sulphur = S

The links joining these atoms together, thus binding them rigidly into molecules of a definite kind, are represented by straight lines. Thus alcohol (the ordinary variety found in intoxicating drinks) is represented by the chemist in the following way :

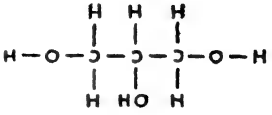


Thus pure alcohol consists of numbers (the total is astronomical even for a small volume of alcohol) of molecules each consisting of two atoms of carbon, six atoms of hydrogen and one atom of oxygen, all joined together in the specific way indicated by the above formula. We need not worry about how these facts are arrived at ; they have been amply demonstrated by long and arduous work extending back for more than a century. For our purpose it is sufficient to recognize that each and every distinct chemical substance, whether it be drug, dye or protein, is distinguished by consisting of numbers of identical units, or molecules, each of which consists of a definite arrangement of atoms. Finally, brief mention must be made of the size of atoms. For many purposes the carbon atom can be regarded as a solid sphere ; the diameter of this is a four hundred-millionth of an inch. The atoms of other elements, and consequently of the multitude of different molecular combinations in which they can exist, are of comparable size. Small though these dimensions are modern scientific methods can measure them with great accuracy, and there is no question of the truth of the atomic theory of matter. It is the very smallness of atoms and molecules which disguises so well the fact that all matter is an aggregate of these minute particles. In everyday operations we deal with quantities of matter containing at the least billions of individual atoms—it is, therefore, not surprising that their existence is not immediately apparent.

Although, as already mentioned, every substance has its own characteristic atomic structure, many groups of substances are known which possess related structures. The formula of ordinary alcohol has been given above. A great many other substances are known, however, which resemble alcohol in possessing the characteristic grouping—O—H. The following are typical " alcohols " :

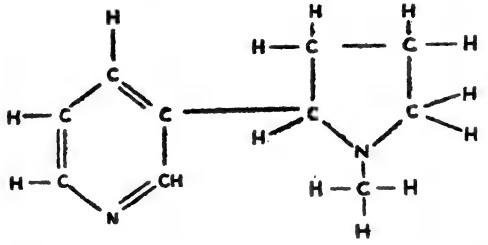


Methyl alcohol



Glycerine

Many drugs derived from plants have similar structures. One major group is that known as the alkaloids, so named because, like the mineral alkalies, they have the power of forming salts with acids. In general the alkaloids are complex carbon compounds distinguished by the presence of nitrogen (N). As in many other compounds of carbon the carbon atoms have a marked tendency to be arranged in rings of six atoms. Nicotine, the active principle of tobacco, is a typical alkaloid and possesses the following structure :

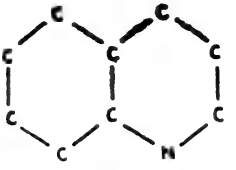


Nicotine

Chemically, nicotine is known by the rather frightening name of a-pyridyl-N-methyl-pyrrolidine, but from the formula above it will be seen that it is built on a comparatively simple and symmetrical plan and contains only three kinds of atoms—carbon, hydrogen, and nitrogen.

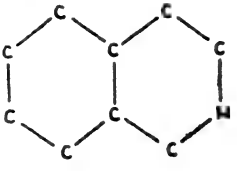
The alkaloids can be further sub-divided according to the main atomic structure of their molecules. Thus a variety

of drugs contain in their molecules the so-called quinoline skeleton :



" Quinoline " skeleton

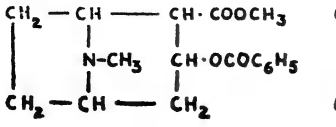
Drugs of this class include quinine, distinguished by its toxic effect on the parasite which causes malaria. Another series of drugs is based on the slightly different *iso*-quinoline skeleton, shown below :



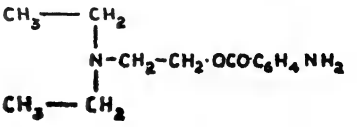
" Iso-quinoline " skeleton

It will be seen that here the nitrogen (N) atom is in a slightly different place. Drugs of this kind include some of those, such as laudanosine, which are present in opium. These drugs differ greatly from those of the quinoline series ; thus many of them have hypnotic properties.

It has previously been mentioned (page 22) that one advantage of isolating pure drugs is that, if their atomic structure can be worked out, it is often possible to prepare similar compounds in the laboratory. Thus the identification of cocaine (A, below) led to the preparation of the very valuable synthetic substance novocaine (B, below). Comparison of A and B will show that there is a considerable similarity in the arrangement of the atoms :



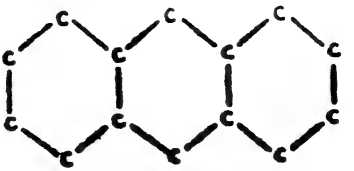
A



B

Although the alkaloids form one of the most important groups of natural drugs, there are many others besides. A great many drugs are even simpler than the alkaloids in that only three kinds of atom—carbon, hydrogen and oxygen—are present in their molecules. An important class of such drugs are those known as the glycosides. In these the active principle of the drug contains in its molecule a molecule of sugar, often glucose. Digitalis, for example, the foxglove drug, contains a number of different glycosides.

Purgatives form an important section in any classification based on medicinal properties. The purgative substances in many drugs contain the same arrangement of carbon atoms in their molecules as does anthracene, a constituent of coal-tar somewhat similar to naphthalene.



Anthracene skeleton

The chemical classification has the advantage, in the many cases in which the pure drug has been isolated and identified, of conciseness and unambiguity. Even when complete identification cannot be effected it is often possible to discover the main plan on which the atoms are arranged and thus to relate an unknown drug to known ones. This is helpful in investigating its pharmacological properties, for it is generally observed that substances with a similar molecular structure have similar physiological effects. Thus, in the first instance, new drugs can be tested on the assumption that their properties are like those of drugs closely akin to them chemically. While this is a fairly good working hypothesis it is by no means universally true, for it not infrequently happens that a change in the molecule, that is, from the chemical point of view, trifling, can have an astonishingly big effect on the medicinal properties of the drug. A striking example of this is described on page 42 where the question of optical isomerism is discussed in relation to quinine and quinidine.

For some purposes it is helpful to consider drugs according to the purposes to which they are put in medicine. The majority of drugs—apart from drugs of addiction—are used in an attempt to restore a sick body to health. The diseases which affect the body are, broadly speaking, of two kinds. There are those which arise, apparently spontaneously, from causes within the body. Among these one may mention certain kinds of heart disorders, mental disease, diseases affecting the sight, and cancer. While external causes cannot be ruled out for such diseases there is rarely any definite evidence for them. Many other diseases, however, are well known to originate from external causes. First among these are those which arise from the invasion of bacteria or micro-organisms. Diseases of this type include diphtheria, tuberculosis, dysentery, and venereal disease. Drugs, can therefore, be classified according to whether they are suitable for restoring disordered mechanisms of the body or whether their purpose is specifically to destroy invading bacteria. Drugs typical of the former class are digitalis and caffeine ; of the latter, quinine and penicillin. The issue is, however, rarely as clear-cut as this, and a great many drugs cannot be strictly assigned to either class. Thus we have the pain-deadening drugs, valuable in surgery, dentistry and diseases such as cancer. These are indirect agents ; they may make possible surgical procedures which the patient could not survive without their help or they make bearable the pains of incurable diseases. The influence of drugs on health may be even more indirect, though no less important, than this. Many diseases are carried by organisms other than those finally attacked. Thus mosquitos carry malaria and vermin carry plague. Substances, such as pyrethrum and derris, which attack disease-carrying insects, are, in the last analysis, just as important as those, such as penicillin, which attack the disease organisms after they are established in the body. Strychnine, as a poisoner of vermin, is just as important as strychnine, the tonic.

Mention of strychnine for poisoning vermin suggests another group of drugs ; those which, while possessing medicinal properties when properly used, are powerful poisons when used in excessive quantities. Thus strychnine itself, besides being a general tonic and a valuable stimulant when

cautiously used, is better known as a poison. As such it has figured in a number of notorious murder cases. Pure nicotine, the most important active substance present in tobacco, is one of the most deadly poisons known. It is widely used in agriculture and horticulture for destroying pests ; incautious use of it in this respect has caused fatal accidents. Nicotine has also been used in suicide and murder. Even so familiar and easily accessible a drug as quinine can produce definite symptoms of poisoning, though in this case the quantities necessary to endanger life are considerable. The majority of drugs derived from plants have some poisonous properties and it is well to recognize this fact when dealing with them. Doctors know the quantities in which they should be used to combine the maximum therapeutic effect with the minimum of ill-effects—the quantities prescribed should therefore never be exceeded.

Chemical warfare is generally regarded as essentially a modern method of fighting. This ignores the fact that many primitive tribes have highly developed techniques for using drugs in hunting and fighting ; arrow poisons are used in many parts of the world, particularly in Africa and South America. The common South American poison is known as curare ; even to-day the method of its preparation is not completely known. It is made under conditions of secrecy and different tribes have different recipes, but species of *Strychnos* enter into its composition. Curare is used for tipping both arrows and the darts fired from blowpipes. Even large animals quickly succumb to the relatively insignificant wounds inflicted by these weapons. The native hunters cut out the flesh immediately surrounding the wound and the rest of the animal can then be eaten with impunity. These arrow poisons have recently been the subject of detailed investigation and from them pure drugs of considerable medicinal value have been isolated. Some of these will be described in a later chapter. *Strophanthus Kombé*, for example, used in the preparation of the African arrow poison kombé, yields the valuable drug strophanthus, similar in its physiological effects to digitalis. Civilized man has thought himself ingenious in using explosives, such as gelignite, for catching fish. When a small charge is exploded in the water fish nearby are stunned or killed and float to the surface, where they can be

collected. Primitive man has known a similar trick for centuries. In South America certain native tribes use the poisonous roots of plants, such as species of *Lonchocarpus*, to produce the same effect. The roots are shredded into the water of pools and the fish are stupefied by poisonous substances contained in them. Large catches are made in this way.

Drugs derived from plants have from time to time been used for judicial and political ends. The Greeks used poisoning by a decoction of hemlock, of which coniine is the most important constituent, as their official method of execution—it is well known that Socrates died in this way. In a subsequent chapter we shall see how a large Mohammedan sect, the Assassins, were to a considerable extent kept under control by the use of the drug hashish. In our own time the Japanese have made extensive use of opium for political purposes. It is well established that they poured the drug into those parts of China which they controlled before being brought to terms by the Allies. In this way they hoped so to demoralize the people that there would be no serious attempt at organised insurrection. So far as can be judged in the present confused state of affairs they were not entirely unsuccessful in this aim.

Mention of hashish and opium brings us to yet another important group of drugs, those generally known as drugs of addiction. Although many drugs derived from plants are of great benefit to man they are, like so many other blessings, often abused. Many drugs have effects on the senses so exhilarating that they are taken for this reason alone. Cocaine has a remarkable effect of sharpening mental perception and inducing an effect of well-being in which the drug-taker feels capable of undertaking any feat, however difficult. Opium and hashish produce a pleasant drowsiness followed by deep sleep characterised by the beauty and pleasure of its dreams. Nicotine, the active principle of tobacco, while milder in effect than either of the above, has a markedly soothing effect. Were these sensory effects the only ones produced by such drugs there could on purely practical grounds be little objection to their use. Unfortunately, however, their continued use leads to most serious mental and physical disturbances. Not the least serious of the properties of such drugs is their habit-forming nature. So great is the craving of the confirmed drug-

addict that the obtaining of the drug becomes the most important thing in life. To obtain it he is prepared to endure humiliations and resort to methods which would be utterly repellent to the ordinary citizen. Continued use of drugs of this kind, such as opium, cocaine, and hashish, leads ultimately to severe demoralization. The physical effects are as serious as the mental. The addict becomes increasingly tolerant of the action of his particular drug so that to produce the effect he desires ever-increasing doses must be taken. So far does this acclimatization proceed that the confirmed addict often takes doses many times greater than those sufficient to kill an ordinary man. This constant ingestion of poisons leads to disorganisation of many natural processes, particularly those of digestion and heart action. The normal fate of the unchecked addict is a miserable death in a mad-house, both his mental and physical faculties damaged beyond repair.

Provided steps are taken early enough addiction can be cured, though the cure is a difficult one. The treatment naturally depends to a considerable extent on the drug involved, but the general procedure is to gradually reduce the daily dose until the patient can dispense with it altogether. One of the difficulties is that, at least in the early stages of treatment, no co-operation is obtainable from the patient who, in severe cases, has virtually no will of his own. With certain drugs, too, such as cocaine, the reduction in the daily dose produces definite physical symptoms and the patient is thus not encouraged to persevere. Nevertheless, if treatment is started early and can be carried out under favourable conditions a cure can generally be effected.

Drug addiction is a most serious problem, both medically and sociologically, but one too large to discuss here in more than general terms. Despite rigid methods of control and drastic punishments, the smuggling and sale of drugs of addiction flourishes throughout the world.

CHAPTER FOUR

QUININE

QUININE is of interest both because of its antiquity—it has been widely used for more than three centuries—and because investigation by modern methods has fully justified the esteem in which it was held by the herbalists who first introduced it into medicine. The history of the drug, although interspersed with much apocryphal lore, appears to be well established as far as the essentials are concerned.

Quinine is the most important of some thirty different alkaloids (page 31) present in the bark of the cinchona tree, which grows wild on the slopes of the Andes, from Colombia southward to Bolivia. Its main value is as a specific against malaria and as such it appears to have become known to the Jesuits in Peru about 1600. Opinion is divided as to whether the natives of the country appreciated its medicinal value. Until quite recently Peruvian Indians, far from using the drug, were prejudiced against it and the only use they could be persuaded to make of cinchona bark was for the dyeing of cloth, a purpose for which the red variety is particularly suitable. Nevertheless, there is every reason to suppose that the Spanish *Conquistadores* became acquainted with the drug through the aborigines ; the native name of the bark, Quina-Quina, which signifies Bark of Barks, certainly indicates that it was esteemed by them.

There is a tradition that the first European to be treated with quinine was a Jesuit missionary who fell ill with fever at Malacotas, a settlement some miles south of Loxa. On his return to the latter town he spread the story of the remarkable properties of the native drug. In the library of a convent at Loxa is said to be a manuscript which shows that about this time (1630) cinchona bark was being generally used by the European colonists of the province. In 1630 the Corregidor of Loxa himself, Don Francisco Lopez de Canizares, fell ill with fever and was restored to health by means of quinine. This success was to have important results. In 1638 the

Countess of Chinchona, wife of the Viceroy of Peru, contracted an intermittent fever. Remembering his own cure the Corregidor of Loxa sent her a supply of the powdered bark by the hand of his own physician, Don Juan de Vega. Again the drug was successful, and her cure appears to have greatly impressed the Countess. On her return to Spain in 1640 she took a supply of the bark with her and seems to have recommended it enthusiastically—so much so that it became known as " Countess's Powder." At the same time it was introduced into Spain by the Jesuits, which earned for it the alternative name of " Pulvis Jesuiticum." In the latter half of the seventeenth century the demand for the powder became very considerable. To their wealthy patients the Jesuits are said to have charged its weight in gold but to the poor they gave it for nothing.

Quinine was introduced into England about 1655 and for many years its history is closely linked with that of Robert Talbor, who made his fortune by selling the drug as a secret remedy for the cure of fevers. While his writings emphasised the dangers of the " Jesuit's Powder " his own secret remedy was, in fact, essentially an infusion of the powder in claret ; occasionally other herb extracts, such as syrup of poppy, were added. So quickly did his fame spread that he was called in to treat, successfully as it proved, a fever from which Charles II was suffering. For this he secured royal patronage and, in spite of his lack of such medical qualifications as were then recognized, he was appointed physician to Charles II and awarded a knighthood. In 1679 he visited France where his fame soon became as great as it was in England. When the Dauphin fell ill with fever his help was sought and again the drug proved successful. For this service he was made a Chevalier. So impressed was Louis XIV that he used every effort to persuade Talbor to sell his secret. The latter at length agreed, with the reservation that the secret should not be disclosed until after his death. When he died, in 1681, Talbor was famous throughout Europe. The secret of his remedy was published in the following year and thenceforward the future of quinine was assured.

The powdered bark was still the only source of quinine and the recognised method of administration was as an

infusion in wine. The great demand for the powder maintained the price at a high level. In 1675 it was about four shillings per ounce. So great indeed was the demand that unscrupulous traders sold instead other powders of an astringent nature, made bitter by addition of aloes. The drug first obtained official recognition in the London Pharmacopœia in 1677, when it appeared under the name Cortex Peruanus. By the early eighteenth century its use was well established in medical practice. James Alleyne, in his New English Dispensatory of 1733, gives several recipes which include quinine. A typical example comes under the heading "Electuarium cum cortice Peruviano Quincei" (Quincey's Peruvian Electuary). The ingredients were as follows :

> "Cort. subtilissime triti (finely powdered bark).
> Serpentariæ Virginianæ (Virginian Snake Root).
> Mithridatii (Mithridate).
> Syrupi de Papav. erratico (Syrup of red Poppies).
>
> Take the bark in fine powder, powder of Virginian Snake Root, Mithridate and Syrup of red Poppies q.s. to make into an Electuary. This is fitted for those agues when the intervals are not very distinct, but there remains some indispositions after the fit is off."

Another electuary compounded of Peruvian bark and syrup of red roses is ". . . almost infallible in all intermittents and is to be given the quantity of a large nutmeg every three or four hours, betwixt the fits."

One of the first signs of botanical interest in the tree was that of Linnaeus, who in 1742 described the genus as Cinchona, in honour of the Countess who had done so much to establish the drug in Europe. In 1753 he gave the species used as the common source of the bark the name *Cinchona officinalis*. It should perhaps be remarked that Linnaeus erred in spelling the name of the Countess ; the error has been perpetuated, however, and this spelling is now in universal use. Botanical interest was stimulated by the fact that the demand for the bark was so great that by the early nineteenth century the native forests had become almost exhausted, a circumstance which was reflected in a rise in price to as much as £5 per ounce. The idea of establishing plantations on their own

Born 1545. at Nampton-wich in Cheshire.
and Died at London about 1607.

John Gerarde (1545-1607), author of one of the best-known of early herbals. (From Johnson's edition of Gerarde's Herbal (1633).)

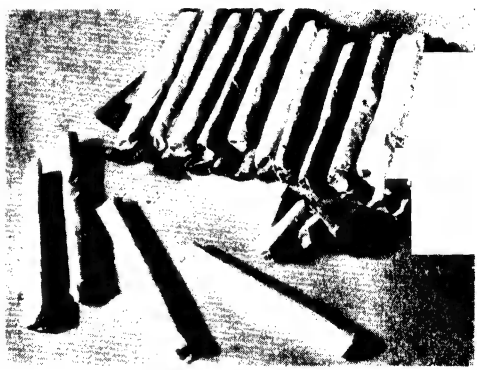
PLATE 11.

Uprooting the Mandrake—see legend on page 14.

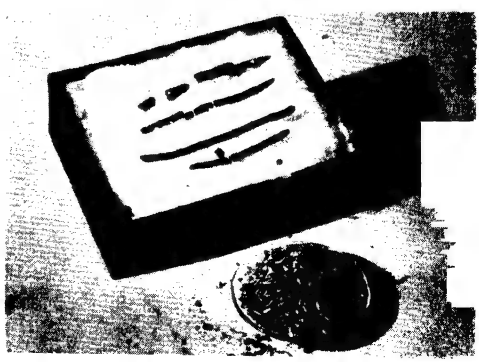
An engraving illustrating the kind of apparatus used for chemical and pharmaceutical work in the 16th century.
... Liber de arte Distillandi de Compositis. *Strassburg, 151.*

A fanciful representation of a herbalist's garden of the early 16th century, also illustrating the kind of apparatus used for distillation.

Crude hemp resin.
(Home Office photograph)

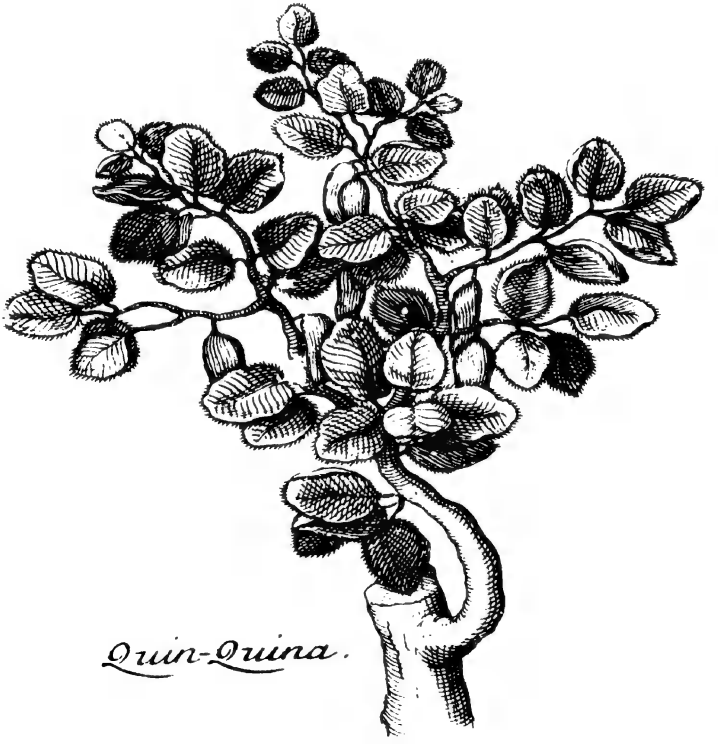


One method of smuggling marihuana (hashish) cigarettes. They are inserted into the folds of corrugated wrapping paper.
(Home Office photograph)



The box contains thin sticks of hashish ready to be inserted into cigarettes. The dish contains kif, the chopped flowering head of the hemp plant, which is mixed with tobacco and rolled into cigarettes.
(Home Office photograph)

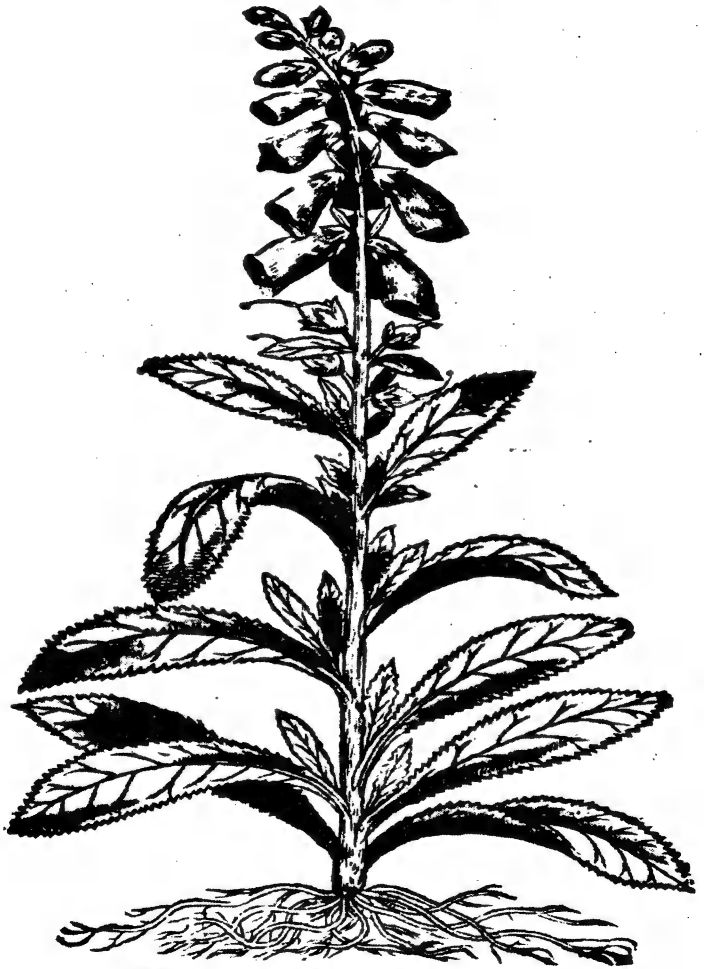
Du Kinquina.



A[illegible] representation of the cinchona tree

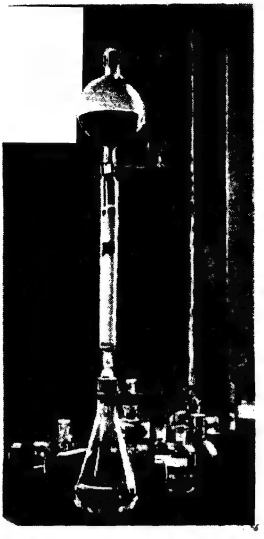
William Withering, who first fully recognized the possibilities and limitations of digitalis,

Digitalis purpurea.



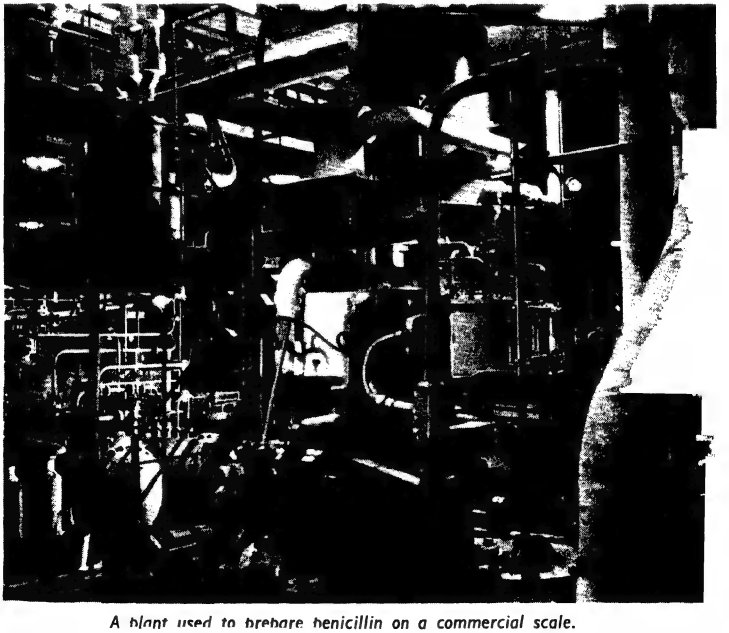
Brauner Fingerhut.

lis purpurea



(Left)
Purification of penicillin by chromatographic analysis—see page 70.

(Right)
Part of the laboratory plant used by the Oxford team of penicillin research workers



A plant used to prepare penicillin on a commercial scale.

PLATE XII.

territories seems to have occurred at about the same time to both the Dutch and the British Governments.

The first seeds were obtained by an Englishman, Charles Ledger, who sent them home to his brother in London. Half were offered to the British Government, but at that time were refused. They were eventually sent, however, to a planter in Ceylon. The other half were offered to the Dutch Government, who paid the sum of only £33 for them.

In Java the Dutch possessed a climate and environment well suited to the growth of the cinchona tree. In 1854 several hundred trees were shipped out there and in spite of some initial setbacks a flourishing industry was founded. Indeed the trees seemed to grow there better than they did in their natural environment and the yields of quinine were often two or three times as great as those normally obtained in South America. Immediately before the last war Java was supplying the bulk of the world's supply of quinine, with an annual export of 15,000,000 pounds of bark.

Cinchona trees were introduced into India and Ceylon in 1859. In Ceylon the experiment proved a failure, but in India a number of plantations were satisfactorily established. The species *Cinchona succirubra* proved particularly well suited to the Indian climate.

South American producers viewed this competition from the plantations with dismay but were quick to realise that their industry could only continue if they followed suit. Accordingly plantations were established in Bolivia, Columbia, Ecuador, and Peru. Here the trees throve, and by refinements in the method of stripping the bark the competition from Java was successfully countered.

The remarkable properties of cinchona bark early attracted the attention of scientists. As long ago as 1792 Fourcroy isolated a crude alkaloid which he named "quina." In 1810 Gomez, a Spanish physician, obtained a crystalline substance which he named "cinchonino." Ten years later Pelletier and Caventon showed the presence of two distinct alkaloids, which they named quinine and cinchonine respectively. Continued research has shown that cinchona bark contains about thirty different alkaloids. The antimalarial properties are due primarily to four of these, known as quinine, quinidine,

cinchonine, and cinchonidine. Of these quinine is the most important.

These four alkaloids fall into two pairs, of which each member bears a curious relationship to the other. The molecule of quinine consists of a complex pattern of atoms of carbon, hydrogen, and nitrogen. The molecule of quinidine has a pattern which is identical, except that it must be regarded as a mirror-image of the quinine molecule. This rather difficult conception may be made clearer by the following analogy. If the molecule of quinine be regarded as a left-hand glove the molecule of quinidine would be represented by the right-hand member of the same pair. Although built on identical plans they are not completely interchangeable. Cinchonine and cinchonidine are related in exactly the same way. This phenomenon is known to scientists as " stereoisomerism " and is of common occurrence. The importance of it is that the left-handed and right-handed members, although showing only slight physical differences, may differ enormously in their biological properties. For example, the body derives its energy from the sugar glucose, which also can exist in left- and right-handed forms. Despite their close similarity only one of the two forms is utilized for the production of energy. In the case of the cinchona alkaloids it is found that while all four show some activity against malaria, the left-handed members are always more active than the corresponding right-handed ones. While a few people are unusually sensitive to quinine, so much so that its use is inadvisable in their cases, they are not generally sensitive to the right-handed quinidine, which can therefore be prescribed with safety.

Ever since quinine was first produced in the pure state more than a century ago chemists have been engaged intermittently in the task of discovering its constitution and finding a method of synthesis. Both these tasks have been accomplished. The arrangement of the atoms in the quinine molecule was finally established in 1908. Since that time much work has been done in the attempt to build up this complex arrangement from simpler ones and for many years a number of chemists were close to the goal. Success was finally achieved in 1944 by two American chemists, R. B. Woodward and W. E. Doering. It must, however, be emphasized that their method of synthesis

is a long and tedious one, involving fifteen different operations. Although their success has brought nearer the day when synthetic quinine will be a commercial possibility the transition from laboratory to factory is likely to take a considerable time, since the present method does not appear to lend itself to economic production.

For some two centuries after its discovery quinine was used only in the crude form of cinchona bark, which contains on an average 2 to 5 per cent of the pure substance. Today, however, pure quinine is almost exclusively used. The powdered bark is mixed into a paste with lime and dried thoroughly. The alkaloids are then extracted with oil or amyl alcohol. From these solvents they are extracted into water by shaking with dilute hydrochloric acid. When the aqueous solution is made alkaline by the addition of soda or ammonia the alkaloids are precipitated and can be filtered off. The precipitated alkaloids are redissolved in dilute acid and the solution is just neutralized with soda. The solution is heated to boiling and then set aside to cool. If the appropriate volume relationships are observed almost pure quinine separates from the solution on standing. It can be further purified by repeated crystallisation in the same way. As quinine itself is almost insoluble in water it is generally used in the form of its soluble sulphate, the salt formed by combination with sulphuric acid.

Many alkaloids, such as strychnine and nicotine, are very poisonous ; quinine owes its valuable therapeutic properties to the fact that, while very deadly to the malaria parasite, in moderate doses it produces no ill-effects in man. Quinine attacks the parasite only while it is free in the blood ; this period corresponds with the bouts of fever in the patient. To be effective, therefore, the drug must be administered at least an hour or two before the anticipated attack occurs. If this is done the fever can generally be averted. For this purpose the dose used is considerable—ten to fifteen grains of quinine sulphate twice or thrice daily. The main use of the drug, however, is as a prophylactic. In fever regions the active symptoms of malaria can be largely avoided by taking a daily dose of quinine—five to seven grains is an average quantity.

Excessive or prolonged use of quinine may give rise to the condition of cinchonism. The symptoms of this closely resemble those found in poisoning by aspirin and related drugs —disturbance of vision, deafness and ringing in the ears are characteristic symptoms. In musical people the latter is said to give rise to very bizarre effects. The possibility of personal idiosyncracy, and its avoidance by use of quinidine, has already been mentioned. For daily use quinine has the disadvantage of a very bitter taste. In certain derivatives of quinine the taste is much less marked, and although they are more expensive and larger doses are required to produce the same effect these derivatives are used quite considerably. They are sold under various trade names such as saloquinine and aristo-quinine.

Although the main use of quinine is in the treatment of malaria it is also a valuable antipyretic, i.e. a drug for reducing the body temperature in fevers other than those of malaria. For this purpose it has the great advantage that it has no effect on the normal temperature of the body ; if the temperature is raised above normal, however, quinine is often effective in restoring it to normal. One of the main factors influencing body temperature is the rate at which the cells metabolize : this in turn is influenced by the rate at which they receive oxygen from the hæmoglobin of the blood. The antipyretic action of quinine may be due, at least in part, to its power of interfering with cellular respiration.

Even this does not exhaust the possibilities of the drug. Because of its bitter taste, which serves to whet the appetite, and its power of promoting digestion, quinine has definite tonic properties and is often prescribed for this purpose.

Quinine is known to increase the tone of the muscles of the womb and for this reason is sometimes prescribed as a general tonic in the later stages of pregnancy. There is a popular, but ill-founded, belief that quinine effectively promotes abortion. It is presumably this that Alleyne had in mind when he wrote in 1733 that it is " suitable for women when the menses are obstructed."

Quinine itself, and more especially certain of its derivatives, has a slight antibacterial effect. (Malaria is caused by an organism, a protozoön, considerably larger than bacteria). Possible uses in this respect are being investigated and already

some antiseptics of this type are on the market. Besides its effect on bacteria quinine has some spermicidal properties and is, therefore, used as the active principle of certain kinds of contraceptive pessary. Its effectiveness for this purpose is commonly much overestimated.

Quinidine, the isomer of quinine already mentioned, besides possessing considerable activity against the malaria parasite has another important medical application. It has considerable value for alleviating the condition known as auricular fibrillation. This is a disorder of the heart rhythm in which the ventricle, the muscular chamber of the heart which pumps blood round the body, contracts rapidly, irregularly, and ineffectively. One symptom of this condition is severe dropsy. We shall see later that the empirical use of digitalis as a cure for dropsy led to the discovery of other drugs which control auricular fibrillation.

The shortage of quinidine during the war years has stimulated interest in fagarine, another plant product which has proved valuable in treating disorders of the cardiac rhythm. Fagarine is a crystalline substance obtained from the leaves and young shoots of *Fagara coco*, a tree which grows in central and northern Argentine. The physiological effects of fagarine are very similar to those of quinidine, and the available evidence indicates that it is an effective substitute for the older drug. Indeed it has been reported that cases of auricular flutter and auricular fibrillation, which failed to respond to quinidine, were effectively controlled by the use of fagarine.

In the years immediately before the last war the production of quinine was a considerable industry ; world consumption for the year 1938 was 15,000,000 ounces. During the war it was necessary for the Allies to maintain large armies in regions where malaria is prevalent and quinine consequently assumed a new importance. The loss of Java, the world's largest producer of the drug, might well have proved a really severe blow had it not been possible to produce, on a vast scale, synthetic drugs such as atebrin and plasmoquin, and more recently, paludrine, which are also specific against malaria. It is at present difficult to foresee how the development of these drugs as a war-time measure will affect the demand for quinine now that peace is restored. The available evidence indicates that

the synthetic substitutes proved highly effective and they are likely to command a considerable part of the trade formerly held by quinine. Paludrine in particular is likely to prove revolutionary because besides being highly effective it greatly reduces the cost of treatment. On the other hand quinine, as indicated above, has several uses apart from the treatment of malaria and it is possible that development of these uses may provide important new outlets.

CHAPTER FIVE

HASHISH

HASHISH resembles quinine in being of great antiquity but here the resemblance ceases. Quinine is one of the most useful drugs known to medicine and countless lives have been saved by its use. In contrast the history of hashish is an almost unbroken record of human misery and degradation. Nevertheless, the story of hashish is one of peculiar interest from both the human and the scientific point of view.

The drug is a product of hemp, *Cannabis sativa L.*, which is of great economic importance both on account of the fibres derived from it and the oil which can be expressed from its seeds. Botanically hemp is of interest because the male and female flowers are borne on separate plants. On the principle that the female of the species is more deadly than the male it is perhaps not surprising to find that it is the female plant alone which produces hashish. The flower head of the female plant is covered with fine hairs, each associated with a tiny gland. From the latter is secreted a green resin and it is this, carefully collected, which forms the crude hashish of commerce. Plants vary considerably in the quality of the hashish they yield. In general it is found that those most suitable for production of fibre and seed are not the most satisfactory for the production of hashish. So great is the demand for the drug that, in spite of the heavy penalties that are inflicted on culprits who are caught, selected varieties are grown throughout Asia, particularly in the Lebanon and Syria, solely for the sake of the drug. In certain preparations the leaves of the flowering head are combined with the resin.

Until quite recently the use of hashish was practically confined to Eastern countries. In India it has been known for well over two thousand years and in some parts of the country it has mystic significance. In China, too, the drug has been used for many centuries, though there is evidence that here it was esteemed as much for its possible medicinal value as for its qualities as a drug of addiction.

The extensive use of hashish as an intoxicant is particularly associated with a curious Mohammedan sect known generally as the Assassins. The modern word "assassin" is derived from the Arabic "hashishin," an eater of hashish. The sect was founded at the end of the eleventh century by one Hasan-i-Sabbah. One of its essential beliefs was that the committing of murder was a certain means of entering Paradise, the more so if the murdered person was an infidel. The sect became notorious, particularly because of their continuous attacks on the Crusaders. When it is realised that at its height the order numbered tens of thousands, with every member an avowed and eager murderer, its menace can be imagined. Their main strongholds were in Syria and Persia, but their influence eventually extended far beyond these limits and they are reputed to have taken part in intrigues as far afield as the eastern states of Europe.

The hashishins were organised very much on monastic lines. At the bottom were the novitiates of the rank-and-file ; at the top were the high-priests entrusted with all the secrets of the order. The supreme head was the ill-famed Sheik-el-Jabal, or Old Man of the Mountains. It is quite possible that the sect was originally founded as a result of genuine religious convictions, however perverted these may appear to modern judgment. It was not long, however, before the leaders saw the immense practical benefit to be reaped from complete control of an army of cut-throats. Thereafter they initiated a programme of merciless looting and murder, in which sadism, greed, and political ambition were the prime motives. So outrageous did their crimes become that they became intolerable to the neighbouring nations, who took energetic measures to suppress them. Their fanaticism, however, made them persistent foes and their power was not finally broken until 1256. In that year the Tartars defeated them decisively and paid them in their own coin by massacring no less than 12,000 of them. Even then isolated groups persisted for many years and it is said that even today the sect is not entirely extinct.

Apart from their historical importance the hashishins are of interest because the whole of their considerable organisation was, to a great extent, held together by the skilful use of hashish. This drug produces effects somewhat similar

to those of opium and the chiefs of the order, who claimed divine power of transporting those whom they favoured to Paradise, implemented their promises by occasionally inducing the exhilarating and sensuous "pipe-dreams" of hashish. The secret of the drug was closely guarded. It is small wonder that the ignorant and deluded novitiates, convinced that death would return them eternally to the Paradise whose joys they had already tasted, would gladly undertake missions which meant almost certain death.

Today hashish is as potent a drug as it was centuries ago and the public knowledge of its properties has created world-wide problems. It is used extensively through Asia, and is a serious administrative problem in Egypt. From Asia its use spread to Mexico and thence to the United States. Western Europe has hitherto been largely immune from serious addiction to hashish, but there is a risk that it may increase during the unsettled conditions following the war. Like kindred drugs its use largely represents an attempt to escape, if only for a brief time, from the worries and cares of daily life. As the latter increase so does the tendency to seek relief through drugs.

Hashish is prepared in a number of forms. As already mentioned either the resin alone may be used or the latter may be combined with a greater or lesser proportion of the plant itself, but however they are made the preparations are taken almost exclusively by eating or smoking. These preparations, fundamentally similar, are known by various names in different parts of the world. In Egypt the name is *hashish*; in India *bhang*, *charas* or *ganja*; in North Africa *kif*; and in both North and South America *marihuana*.

The effects of the drug vary greatly from one individual to another, more so perhaps than with any other known drug. This may be due in part to the fact that owing to the illegality of its use, which means that it must be prepared under conditions of strict secrecy, different preparations contain different combinations of active principles. As will be shown later the effects of hashish are almost certainly not those of a single substance but those of a complex mixture of drugs. From the few available written descriptions of the effects of hashish it is difficult for the non-addict to appreciate the reason for the ease with which it obtains a grip on its users. The symptoms

described seem bizarre, unpleasant, and frightening. One writer, Gautier, describes how it seemed to him that his body had become dissolved and transparent, so that he could clearly see in his stomach the hashish he had swallowed. The friends who were with him appeared as half men and half plants, while when one of them spoke to him in Italian the hashish transposed it into Spanish. After a few minutes he recovered completely and thereafter suffered no ill-effects. Another person told how he experienced a remarkable feeling of elasticity so that he was able, as he thought, to enter a bottle through its neck and remain in it quite at his ease. To yet another it seemed that he had become the piston of a steam-engine. While such symptoms would be expected to discourage the potential addict there is no doubt that through incautious use an insatiable craving for the drug develops quickly. The established addict will stop at nothing in his efforts to obtain further supplies. Consequently the price is very high and unscrupulous dealers even take a leaf from the book of the hashishins and compel their victims to commit crimes as the price of the drug. In the United States marihuana cigarettes are said to fetch as much as £1 a piece. So ruthless are the dealers in this vile corruption of mind and body that it is reported that they have even tried, and not entirely without success, to sell the drug to children of high-school age.

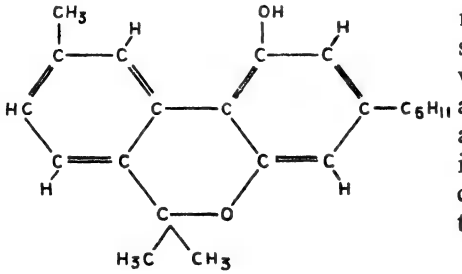
Since 1945 hashish has presented a particularly serious problem in Egypt, following an exceptionally heavy crop in Syria and the Lebanon. In previous years the high price of the best quality hashish, about £7 per ounce in 1944, had successfully kept the drug out of the reach of the poorer sections of the population. For the latter its use can to some extent be excused because of the relief it is said to give to the severe internal disorders consequent on drinking Nile water. Nevertheless, it is undoubtedly better to take steps to purify drinking water than merely to deaden with a dangerous drug the pain due to foul water. In normal years the illegal growth of hemp for hashish in Syria and the Lebanon is greatly restricted by the activities of French or British patrols. Owing to the war, however, these patrols were very much restricted, with the result that greatly increased quantities of hashish began to be smuggled into Egypt. Because of its abundance

the price fell considerably in 1945 and it thus came within reach of a considerable portion of the population. The famous Russell Pasha—Sir Thomas W. Russell, chief of the Central Narcotics Intelligence Bureau at Cairo—is tackling the problem by every possible means suggested by a life-time in combatting drug smuggling, but it is as yet too early to say how much the war has affected hashish addiction in Egypt or elsewhere. Certainly the general result has been to increase it.

The mental effects of hashish, already briefly mentioned, are so variable, sensuous, and grotesque that they do not lend themselves to scientific classification. In describing the physical effects of the drug, however, we are on surer ground. There is good evidence that its effect is primarily on the central nervous system ; that is to say, the part of the nervous system comprising the brain and spinal cord. Apart from the hallucinations which may take so many different forms, the effect of the drug is to cause alternations of exaltation and melancholia, and distortion of time and place. Its use is often followed by a brief but complete coma. Its effects on animals have been carefully investigated and this research has led, among other important results, to a satisfactory method for the biological assay of hashish preparations. In one method the drug is estimated by observing its anæsthetic effect on the cornea of the rabbit's eye. In dogs hashish causes the condition known as ataxia (failure to control muscular movements) and this effect also has been used for purposes of essay.

Compared with the long use, or abuse, of hashish as a drug of addiction, its chemical and pharmacological investigation, although started nearly a century ago, is of relatively recent date. In 1857 two brothers, H. and T. Smith, found that the activity of hashish preparations could be greatly concentrated by extracting them with alkali, in which the active principle was not soluble. They showed, too, that the active residue was free from nitrogen. The latter observation was of particular interest because it showed that the pure drug was not an alkaloid (see note page 31). It thus differed from the majority of drugs, such as opium, quinine, and nicotine, known at the time. For many years little further progress was made. Between 1895 and 1900 a number of investigators obtained, from the residue left after extraction with alkali, a

pale yellow oil which they named cannabinol after the botanical name of the plant, *Cannabis sativa*. Not for some thirty years, however, was it shown conclusively that cannabinol was not a pure substance as was at first supposed. Considerable further progress was made by Cahn, who went far towards establishing the chemical identity of cannabinol, which he obtained in the pure state. The work was carried further by Todd and Adams, working in Great Britain and the United States respectively. Cahn had shown that cannabinol must possess one of twelve similar structures. Todd and Adams were able to limit the possibilities to only two. The final solution of the problem came from the isolation of a second substance similar to cannabinol. This was named cannabidiol. For various reasons it was possible to identify cannabidiol unequivocally. From an investigation of the relationship between cannabidiol and cannabinol the precise structure of the latter was determined. The arrangement of the atoms in the molecule is shown in the accompanying illustration.



Curiously enough cannabinol, on isolation in the pure state, proved to be without any of the physiological properties of hashish.* The main physiological effects are, however, obtained when the molecule of cannabinol is slightly modified by the addition of four hydrogen atoms, thus converting it into tetrahydrocannabinol. It is in this form that it exists in hashish itself. This substance, like quinine, can exist in both left-handed and right-handed forms, and these differ considerably in their biological properties. The left-handed form is several times as active physiologically as the right-handed. Nevertheless, even the pure left-handed form is not so active as highly purified natural resin, so it is obvious that part of the

* Some very recent work, however, indicates that it does possess slight hashish activity.

CHAPTER SIX

DIGITALIS

THE common purple foxglove—*Digitalis purpurea*—is the source of the drug digitalis, long recognized to be of great value in the treatment of certain kinds of heart disease. Digitalis is said to have been introduced into the continent of Europe by Irish monks, and it is interesting that after long dependence on imported supplies war-time conditions made us once again turn to our own native resources. During the war years leaves of the wild foxglove were extensively gathered, mainly by school children, and after drying and powdering were used for preparing the tinctures commonly used in medicine.

The history of digitalis provides a striking example of the way in which valuable scientific information can emerge from the mists of folk-lore and superstition. The drug seems to have been used, though not always for the proper purpose of treating heart disorders, from very early times. The present name of the plant is said to be derived from "foxesglew," found in some of the early Anglo-Saxon herbals. In the eleventh century it is mentioned as "foxes glofa" and in the thirteenth as "foxesglove."

Preparations containing foxglove were included among the nine hundred prescriptions used by the mysterious Welsh Physicians of Myddrai. The early history of these people is obscure but their existence in mediaeval times is well established. The founder of the family was named Rhiwallon ; his father was named Gwyn, the only son of a farmer's widow, and his mother is reputed to have been a nymph of the Lake of Llyn y Van Vach. Despite this myth it is clear that from early times, possibly as early as the reign of Hywel Dda, there lived at Myddrai a family in which medical lore was handed down from one generation to the next. Their herbal recipes were apparently first written down in the eleventh century, under the patronage of the Lord of the Manor of Rhys Gryg. The

last of the physicians, who claimed direct descent from Rhiwallon, died only in the nineteenth century.

The Bavarian physician Fuchs demonstrated the value of digitalis in the treatment of dropsy, a common result of cardiac disorders, in the sixteenth century. In his "Plantarum Omnium Nomenclaturae" of 1541 he gives foxglove the latinized name of digitalis, deriving it from the German name Fingerhut (or fingerstall) which is based on the appearance of the flowers.

Gerarde, in 1597, states that foxglove is valuable in "extenuating tough flegme or viscous humours troubling the chest," but adds that "there are few physitions use it and it is in a manner wholly neglected."

In the seventeenth century foxglove was used in Somerset for treating fever, but it was regarded then as too dangerous a drug for general use. This need for caution is well recognized in modern medical practice, as we shall see later. Nevertheless, digitalis was admitted to the London Pharmacopœia in 1722, chiefly on the recommendation of the English herbalist William Salmon. Salmon, too, recognized its value for treating dropsy but, like Gerarde, also acclaimed it as a sovereign remedy for consumption (tuberculosis). This error probably arose from confusion between tuberculosis, for which digitalis is quite ineffective, and dropsy of the chest, which it relieves rapidly. Unfortunately this error was perpetuated and did much to bring the drug into disfavour later. It finally disappeared from the pharmacopeias for many years, being regarded as a dangerous poison, which indeed it is unless skilfully used.

Chief credit for the reintroduction of digitalis and full recognition of its powers and limitations goes to another English physician, William Withering, who practised medicine first in Stafford and later in Birmingham. His interest is said to have been aroused by a statement by one of his patients that throughout Shropshire a concoction containing foxglove leaves was used to cure dropsy. He showed that when properly handled, and with a dose carefully controlled for each patient, digitalis would in fact cure dropsy. Recognition of the very varying response of different individuals was of the greatest importance; there is no universal standard dose. While Withering was describing the real value of digitalis, most of

his contemporaries were still using it for the treatment of tuberculosis and it is ironical that even after his death in 1799 this false conception persisted and his work was largely ignored. Withering published his conclusions in 1785 in a book, now very rare, *An Account of the Fox-Glove and some of its Medical Uses.*

Further advances followed the discovery of the cause of " the dropsy." It is associated with the condition now known as auricular fibrillation, a disorder of the heart rhythm. The ventricle, the muscular chamber of the heart whose contractions pump blood around the body, contracts rapidly, irregularly, and ineffectively. Many of the contractions are so weak that they produce no pulse. In severe cases the circulation is so poor that the action of the kidneys is impaired and large quantities of water accumulate in the body. Digitalis cures the resulting dropsy by restoring the normal action of the heart. The heart-beat is slowed, the contractions are stronger and the circulation improves. After a few weeks urinary secretion increases and the patient, previously bedridden, is able to walk and even to do light work. Recognition of the way in which digitalis works, a piece of research with which the name of Sir James Mackenzie is particularly associated, made possible the effective use of the drug in medicine. Today it is regarded as the most valuable of all drugs used in the treatment of this kind of heart disease.

It has already been mentioned that individuals differ very greatly in their reaction to digitalis. Treatment can, therefore, only be satisfactorily continued if standardized material is available so that, when tolerance is established, a uniform daily dose can be maintained. In this country digitalis preparations, which vary greatly in their potency according to the locality and method of collection, are standardized by means of tests carried out on cats. The unit of potency is defined as the quantity required to stop the heart-beat in an anæsthetized cat. In the United States the unit is defined as the quantity required to kill a frog of 25 grams weight.

The chemical nature of digitalis has been very closely investigated and its pharmacological action has been shown to be due to a number of constituents, of which the most important is digitalin. Other pharmacologically active constituents,

chemically closely related to digitalin, are digitonin and digitoxin. These substances differ markedly from quinine, and other drugs of the alkaloid type, in that they contain no nitrogen. Their molecules contain only three kinds of atom—carbon, hydrogen, and oxygen. The molecules of digitalis drugs consist of a complex molecule, known as a steroid, joined to a much simpler molecule of sugar. In the body the sugar fraction is slowly split off and the active steroid fraction is released.

It may be mentioned that other important natural substances have molecules chemically similar to those of the digitalis drugs, though differing very much from the latter in their physiological action. They include the sex-hormones and vitamin D.

Certain other natural substances produce effects similar to those of digitalis and are also used in medicine. Among these may be mentioned squill—which Robert Burton regarded as a cure for melancholy—which consists of the sliced bulbs of a plant of the lily family. Certain arrow poisons used by native tribes—such as kombé of Africa and ouabain of South America—have an action similar to that of digitalis, and their medical use has been developed.

When properly handled digitalis is a most valuable drug, but like many other drugs it is open to improper use. It has been used at least once for murder. Extensive use of the drug for criminal purposes was revealed a few years ago in connection with a widespread insurance swindle in the United States, where it is customary for life-insurance companies to insure against total and permanent disability. During the slump of 1931 certain firms of lawyers persuaded policy-holders to submit fraudulent claims. More than a dozen doctors were involved and their part was to teach prospective claimants to simulate heart attacks. Digitalis was administered to produce changes in the heart rhythm and so to deceive reputable specialists briefed by the insurance companies. The fraud was eventually discovered only because of the excessive greed of the swindlers; suspicions were aroused because of the abnormally large number of comparatively young men who submitted claims for compensation based on a kind of heart disease rarely found in men below their fifties. Some forty

different companies were victimized and the policies involved totalled more than ten million dollars. Altogether the companies paid out several hundred thousand dollars before the swindle was discovered.

CHAPTER SEVEN

PENICILLIN

THE aura of romance surrounding penicillin—its production by a mould accidentally grown on a bacterial culture ; the failure of the first attempts at purification ; the re-investigation of the problem by the Oxford team of workers ; their demonstration of the unique properties of penicillin ; its commercial development despite the difficulties of war ; and the final success of large-scale production just in time to play an important part in the invasion of Europe—have tended to obscure and distort the scientific background of the work. Furthermore, partly as a result of the war-time necessity for banning the publication of the results of research, the facts relating to the discovery and early history of penicillin have often been incorrectly stated with the result that an over-abundance of credit has been given to some workers, to the detriment of others. In this chapter an attempt is made both to summarize present knowledge of penicillin and to remove some popular misconceptions relating to it.

One such popular misconception is that Professor Sir Alexander Fleming's discovery of penicillin introduced a new principle into medicine. In fact this is far from the truth. That many species of bacteria and fungi produce substances poisonous to other microbial species was well known at the end of the nineteenth century and even then progressive thinkers had conceived the idea of making use of such microbial antagonisms to destroy the bacteria which cause disease in man. As long ago as 1887 Pasteur, the father of modern bacteriology and his colleague Joubert used the phenomenon of antagonism—or *antibiosis* as it is now called—to control anthrax in animals. They found a bacterial species which produced a substance—or antibiotic—which killed the anthrax bacillus. Of the anthrax organism they wrote :

> Neutral or slightly alkaline urine is an excellent medium for the bacteria (of anthrax). . . . But if when the urine is inoculated with these bacteria an aerobic

organism, for example, one of the 'common bacteria,' is sown at the same time, the anthrax bacteria make little or no growth and sooner or later die out altogether. It is a remarkable thing that the same phenomenon is seen in the body even of those animals most susceptible to anthrax, leading to the astonishing result that *anthrax bacteria can be introduced in profusion into an animal, which yet does not develop the disease* ; it is necessary only to add some 'common bacteria' at the same time to the liquid containing the suspension of anthrax bacteria. *These facts perhaps justify the highest hopes for therapeutics.**

About this time other workers reached the same conclusion. Babès "studied experimentally the way in which bacteria . . . produce chemical substances . . . in such a way as to harm bacteria of other species" and considered the possibility of using this phenomenon therapeutically. Catani (1885) used cultures of an organism which he called *Bacterium termo* to treat human tuberculosis. A Swiss bacteriologist, Garré, also had similar ideas.

In 1889 another research worker, a German named Doehle, deliberately carried out an experiment which produced a result strikingly similar to that which Fleming, as we shall see later, observed on his accidentally contaminated bacterial culture. Doehle mixed anthrax bacilli into melted gelatine and poured the mixture into a flat, sterile dish. In the surface of this jelly he then planted a square of gelatine containing a species of bacteria which he named *Micrococcus anthracotoxicus.* The latter produces a substance, poisonous to anthrax bacilli, which diffuses out into the gelatine. The result was that when the bacteria grew the square containing the *Micrococci* was surrounded by a zone of clear gelatine in which the anthrax bacilli had not grown. In precisely the same way Fleming, forty years later, was to observe that staphylococci (bacteria common in septic wounds) would not grow near a colony of the mould *Penicillium notatum.*

Also in 1889 a French research worker, Bouchard, found that yet another microbial species, *Pseudomonas pyocyanea,*

* This translation from Pasteur's work is quoted from the Lister Memorial Lecture, delivered by Professor Sir Howard Florey on October 11th, 1945. Italics are mine.—T.I.W.

inhibited the growth of the anthrax bacillus and found that it could be used with some success to control anthrax in rabbits. In the following year Honl and Bukovsky, two Russian workers, used preparations of *Ps. pyocyanea* to treat septic ulcers and were most enthusiastic about the results. Ten years later Emmerich and Low were using a preparation they called " pyocyanase " to treat a variety of infections in animals. These workers made an elementary, though vitally important, contribution to the subject by stating in unmistakable terms that an effective chemotherapeutic agent must be a *specific* poison of bacterial cells and possess a low toxicity towards animal cells.

In 1896 Gosio obtained from a mould a substance, which he called mycophenolic acid, in the pure crystalline state—an important event in the history of antibiosis.

At the turn of the century Lode (1903) and Frost (1904) independently made detailed studies of the phenomenon of antibiosis and antagonism between micro-organisms and added greatly to our knowledge of this subject.

Later Nicolle, in France, showed that several bacterial species produced substances which inhibited the growth of the deadly tubercle bacillus and used them, apparently with some success, to prevent tuberculosis in guinea-pigs. Another Frenchman, Vaudremer (1913), carried out similar experiments with cultures of the mould *Aspergillus fumigatus* ; it is a matter of considerable interest that recent work has shown that this mould produces four different antibacterial substances of which at least one—helvolic acid—inhibits the growth of the tubercle bacillus.

These lines of research progressed steadily. It was well established that substances produced by one kind of bacteria or fungi could be deadly to bacteria which cause disease and that use might be made of this fact in controlling bacterial infections in man or animals. Nevertheless, the problem was never quite solved, partly because bacteriological and clinical technique was not well enough established ; because the chemical methods of purifying and stabilizing the antibacterial substances had not been worked out ; because, as we now know, the antagonisms investigated were not the most favourable ; and probably also because none of the workers con-

cerned had the necessary tremendous confidence in his results to overcome the many obstacles, both practical and theoretical, which lay ahead.

In 1921 Lieske showed that certain soil organisms, actinomyces, produced antibacterial substances. Gratia and Dath, in France, followed up his work and found many new antagonists. In 1925 Zukerman and Minkewitsch, Russians, found on a culture of a diphtheria-like organism a contaminant which produced an inhibitory substance. They identified the contaminant as a bacterium known as *B. mesentericus vulgatus* and showed that fluids on which it had grown could be used to protect guinea-pigs against diphtheria infection.

From this brief historical account it will be seen that the way had been well paved for Fleming's discovery of penicillin in 1929. As in the case of Zukerman and Minkewitsch the actual discovery resulted from a combination of good fortune and acute observation. During the course of routine work a culture of *Staphylococcus aureus* (bacteria which are a common cause of septic infection) became contaminated with a mould which had grown from a spore which had entered the culture from the air of the laboratory. In the ordinary way such a contaminated culture would be discarded but a peculiarity in this particular instance caught Fleming's eye and he retained the culture for further examination. He had noticed that round the colony of the mould—a fluffy patch similar in appearance to those which grow on mouldy cheese or bread—the colonies of staphylococci had disappeared. It was clear that he had discovered another example of microbial antagonism, in this case between a mould and a bacteria, and as he was interested in this phenomenon he investigated it further. On careful examination the mould was identified as a species known as *Penicillium notatum*. It grew readily on a variety of nutrient media, such as the broth on which many species of pathogenic bacteria are commonly grown in the laboratory. Broth on which the mould had grown, filtered free of the mould itself, inhibited the growth of many kinds of bacteria, particularly the staphylococci and streptococci which cause septic infections. It was therefore clear that during growth the mould had secreted into the liquid some substance toxic to the bacteria. Its activity was evidently considerable, for the

inhibitory power of the filtered broth was still detectable even when it was diluted as much as 800 times. Fleming named the active broth penicillin — today this name is applied not to the broth but to the active substance dissolved in it. By experiments with animals he showed that the broth was no more toxic to them than ordinary untreated broth, and he realised that it had possibilities for the treatment of local infections such as septic wounds. He used it extensively, too, as an aid to bacteriology. It must be understood that penicillin is active against only a limited number of bacteria and there are many species which are quite insensitive to it. It therefore provides the bacteriologist, who most often wants pure cultures of bacterial species, with a useful means of eliminating some of those he does not want.

Fleming's observations led to an attempt, by Professor Harold Raistrick and his collaborators at the London School of Hygiene and Tropical Medicine, to isolate the active substance from the broth. They showed that the mould could be successfully grown, with production of antibacterial activity, on a purely synthetic medium consisting of mineral salts and a sugar. They very soon found that the active principle was very unstable, being quickly destroyed under comparatively mild conditions of heat or acidity and in other ways. They found that on acidification of the crude culture fluid the penicillin could be extracted, though not without loss, into an organic solvent such as chloroform. For further purification this represents an important step, but at that time no further progress was made. It was considered that the evident difficulties of extraction, arising primarily from the instability of penicillin, did not justify further work on the problem and it was shelved. Recognition of this fact is most important in understanding the true history of penicillin. At the time there was not, and could not be on the work done, any realisation of the really remarkable properties of penicillin. There was nothing to suggest that further investigation of the antagonism between *P. notatum* and pathogenic bacteria would be more fruitful than had been the results of other investigations of other cases of antagonism. Had the real nature of penicillin been apparent at that time every possible effort would, of course, have been made to continue the work

then. By sheer bad luck Fleming and Raistrick gave up when they were almost on the verge of making a further step which might have allowed them to complete the penicillin story themselves. As events have shown, however, it fell to them to write only the introduction. Interest in penicillin lapsed for several years and was renewed elsewhere, further research being undertaken at Oxford in 1938.

To the layman it may seem strange that penicillin could so well mask its properties. One important reason has already been given, namely that there was little to distinguish the broth containing penicillin from broth containing anti-bacterial substances produced by other moulds. As already described a number of the latter had been investigated during earlier years, but without any very interesting practical results being obtained. Another important reason was that at the time of the first work on penicillin the medical world as a whole was not quite ready to accept the possibility of using chemicals on a really extensive scale for the treatment of disease. It is true that salvarsan (Ehrlich's 606) had been successfully used for the treatment of syphilis, but results were not altogether satisfactory owing to the smallness of the margin between an effective dose and one harmful to the patient. A great number of antiseptics had been investigated in the hope of finding others which would be used in the same way as salvarsan but for attacking different diseases. Many antiseptics were known which could be used for the control of purely local infections, for sterilising surgical instruments, and for similar purposes, but they possessed properties which ruled out their use against infections involving the body as a whole. In general it was found that when introduced into the bloodstream, a necessary preliminary to reaching general systemic infections, antiseptic substances proved as deadly, if not more so, to the patient as to the bacteria. They were, in fact, general rather than specific poisons. The remarkable effects of penicillin are due to the fact that it is not only more active against certain types of bacteria than any other known substance, but that it combines this property with a complete absence of toxicity towards man. This combination of properties is to be found, although to a considerably less extent, in the sulphonamides. The successful use of these very valuable drugs during the 1930's was not only

of great practical benefit but also demonstrated beyond possibility of doubt that many, and possibly all, bacterial diseases could be overcome by chemical agents. This knowledge, which was denied to Fleming, must inevitably have been a source of considerable encouragement to the workers who later took up the task at Oxford.

The work of Fleming, Raistrick and their collaborators completed what may be called the discovery phase in penicillin. They showed that the mould *Penicillium notatum* produced a substance active against certain bacteria causing diseases. No absolute value could be given to the anti-bacterial activity because they had no means of telling how much pure penicillin the broth contained. Fleming made some use of the penicillin-containing broth for treating local infections, and found it a valuable material as an aid to practical bacteriology in the laboratory. Raistrick and his school showed that penicillin was very unstable and made one important step in the isolation process by bringing the active substance from the broth into an organic solvent.

The discovery phase ended in 1932 or 1933, and serious interest was not revived until 1938. In that year Professor Howard Florey and Dr. E. Chain, of the Sir William Dunn School of Pathology, Oxford, became interested in the general problem of antagonisms between micro-organisms. At that time they did not anticipate doing more than adding to, and clarifying, knowledge of a relatively obscure branch of science ; certainly they could not foresee the sensational results to which their work was to lead. In their study of the previously published literature their attention was attracted by the reports of Fleming and his successors on penicillin. Despite the difficulties which earlier workers had encountered it was decided to make a determined new effort to isolate penicillin from the crude fluid on which the mould had been grown. It should be mentioned, however, that workers at the Oxford laboratory have not confined their attention to penicillin. From other moulds they have isolated a number of antibacterial substances including claviformin, helvolic acid, and proactinomycin.

The problem before the Oxford team of workers was a formidable one. The starting point was the observation that

if a certain species of mould, *Penicillium notatum*, was grown on a sugar solution the latter gradually acquired the power of inhibiting the growth of certain kinds of bacteria. Their aim was in the first instance to extract the active principle, penicillin, from the liquid and later to investigate its suitability for use in medicine.

At an early stage in the work it became apparent that the complexity of the problems involved would call for the collaboration of specialists in several different fields of science. Professor Florey, therefore, called for the help of members of his department and recruited assistance from other laboratories. Professor A. D. Gardner collaborated throughout on the bacteriological aspects of the work and Dr. Margaret Jennings on the biological investigations. The chemical investigations were initiated at the Dunn School of Pathology by Dr. Chain and Dr. E. P. Abraham, and after 1942 were continued in collaboration with Professor Sir Robert Robinson and Dr. Wilson Baker (now Professor Wilson Baker, University of Bristol) of the Dyson Perrins Laboratory, Oxford. Dr. N. G. Heatley and Dr. A. G. Sanders devised and built the laboratory plants for the extraction of penicillin and the former developed the method of assay now in general use. When the stage of clinical investigation was reached the first observations were undertaken by Dr. C. M. Fletcher and later by Dr. M. E. Florey, Professor Florey's wife. The above is the team which broke the back of the penicillin problem. At a later date, when the major difficulties had been overcome and it had become clear that penicillin must be commercially developed both for humanitarian reasons and for the war effort, the help of hundreds of other scientists had to be enlisted, both here and in the United States. Though the work of many of these was important, and often brilliant, they cannot be reckoned among the pioneers.

In the investigation of penicillin, as is most often the case in the isolation of substances whose main interest lies in their biological properties, one of the first tasks was to devise a satisfactory method of assaying it so that the fate of the penicillin at every stage in the purification process could be followed. The method finally chosen was one devised by Dr. Heatley, based on the results of previous workers.

It will be remembered that the discovery of penicillin resulted from Fleming's observation that around the colony of mould on his staphylococcal culture the bacterial growth had been inhibited. The inhibition was due to the production of penicillin by the mould and its diffusion into the jelly on which the bacteria were growing. Clearly the more penicillin the mould produces the larger will be the zone of inhibition surrounding it. By measuring the size of the zone a measure can be obtained of the amount of penicillin present. In Heatley's method sterile, nutrient jelly contained in a flat Petri dish is seeded, under standardized conditions, with a bacterial species which is sensitive to penicillin. The organism generally used is *Staphylococcus aureus*, commonly found in infected wounds ; *B. subtilis*, a soil micro-organism, is also often used. If such a seeded plate is incubated at blood heat for ten to twelve hours its surface becomes covered with a uniform dull film of bacterial growth. To assay penicillin solutions small glass or porcelain cylinders are placed on the seeded plate and filled with the solutions to be tested. The plate is then incubated ; the penicillin diffuses out and each cylinder becomes surrounded by a circular zone of clear jelly on which no bacterial growth has taken place. By measuring the diameter of this circle, and comparing it with that produced under the same conditions by a solution of standard strength, the antibacterial activity of unknown solutions can be compared. This method of essay has an accuracy, in the hands of a careful worker, of about 10 per cent.

In the early days of the work the unit of penicillin was arbitrarily chosen as that quantity of penicillin contained in 1 cubic centimeter of a certain solution kept in the laboratory at Oxford. This unit has become known as the Oxford or Florey unit. At a later stage, when pure crystalline penicillin was available, a more exact definition became possible. At an international conference held in London in November, 1944, the pure sodium salt of penicillin was assigned an activity of 1,650 units per milligramme. The international unit is, therefore, now 0.61 microgrammes of pure sodium penicillin. (1 microgramme is one millionth of a gramme. 1 gramme is approximately one-thirtieth of an ounce). This unit is very nearly equal to the original Oxford unit. So great is the

activity of penicillin that as little as 0.01 units of pure material in one cubic centimeter of solution will inhibit the growth of the most sensitive organisms.

The development of a satisfactory method of assaying the activity of unknown penicillin solutions made possible an investigation of the conditions under which the mould gave the best yields of penicillin, and an investigation of its stability under various conditions, as a preliminary to attempts to isolate pure penicillin.

The early work by Fleming had shown that the mould grew well on a nutrient medium consisting only of a solution of sugar (glucose) and mineral salts. When grown at about 70°F. the surface of the solution is covered in a few days with a matted sheet of the mould and the liquid beneath it becomes yellowish-brown in colour. It must be realized that, besides penicillin, the mould secretes into the liquid a very large number of other substances, such as pigments and proteins. Quantitatively these far exceed the yield of penicillin, a fact which adds greatly to the difficulty of extraction. The antibacterial activity reaches a maximum in six to eight days and then diminishes rapidly. To obtain maximum yields it is therefore necessary to harvest at this peak period.

Penicillin production in many ways resembles brewing in which the yeast is replaced by the mould *Penicillium notatum*. An important difference, however, is that while brewing can satisfactorily be carried out in open vessels this is not possible in penicillin production. The air contains spores of many different microorganisms, both bacteria and fungi, which thrive on the same kinds of nutrient solutions as favour the growth of *P. notatum*. As many of these produce substances which rapidly destroy penicillin they must be most rigorously excluded. This maintenance of sterility is the greatest single difficulty in preparing penicillin on an industrial scale. In the laboratory the most satisfactory method of overcoming it has been to grow the mould in previously sterilized vessels plugged with cotton wool. The latter allows access of air, necessary for the growth of the mould, but filters out all particles of dust.

At Oxford and elsewhere scores of different nutrient solutions have been investigated in attempts to increase penicillin yields. Unfortunately there is at present no logical

method of tackling the problem and the research has been guided very largely by trial and error methods. It has been found that very tiny variations in the composition of the solution can have very large effects on the yield of penicillin. For example, the use of ordinary tap-water, which contains traces of mineral salts, instead of distilled water, may cause a considerable change in the yield.

The greatest single advance in the investigation of nutrient media, and one which was of crucial importance in persuading American industrialists to undertake commercial production of penicillin, was the discovery, made in America at a later stage in the work, that yields several times higher than any previously recorded could be obtained by growing the mould on corn steep liquor. The latter is a waste product of the milling industry, in which it results from the bleaching of grain with a solution of sulphur dioxide, and is obtainable cheaply in large quantities. Still better results are obtained if a little lactose (milk sugar) is added to the solution. A lactose-corn steep liquor medium is now almost universally used for penicillin production. On this solution peak activities of several hundred units per cubic centimeter are consistently obtained, as compared with yields of the order of 10 to 20 units on the original medium.

With the development of a satisfactory method of assay and the discovery of the conditions necessary for a good yield of penicillin, it was possible to go ahead with the main problem of extracting pure penicillin from the crude liquid on which the mould has been growing. Fleming, and Raistrick and his collaborators, had previously noted the great instability of penicillin. It is rapidly destroyed by weak acids, weak alkalies, by heating, and by a variety of chemical reagents. If the solution is cooled nearly to freezing and made slightly acid and then quickly shaken with ether, a solvent which does not mix with water, the penicillin passes into the ether with comparatively little destruction due to the acidity. A considerable number of the impurities, though by no means all, remain in the water and can, therefore, be thrown away with it. The penicillin can be extracted satisfactorily by solvents other than ether. Chloroform and amyl acetate are particularly satisfactory ; the latter is widely used in industry. By again shaking

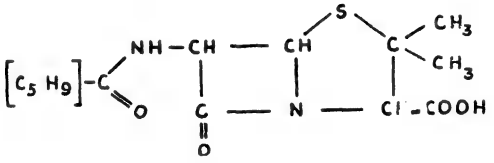
with a neutral watery solution the penicillin can be removed from the ether, or other solvent, again leaving some impurities behind. By continuous repetition of this process, transferring the penicillin from one solvent to another, a good deal of the inactive impurities can be got rid of, though some of the penicillin is unavoidably lost at the same time and there is a limit to the degree of purification that can profitably be achieved.

For further purification extensive use was made of an analytical method, chromatography, which is of comparatively recent introduction into chemistry. Discovered in 1906 by a Russian botanist, Tswett, it remained in obscurity until about 1930, when the increasingly adventurous excursions of chemists into biological and medical fields provided problems particularly suitable for its use. The essence of the method is as follows : A solution of a complex mixture, such as the penicillin solution obtained by the method just described, is allowed to percolate through a column of absorbent, generally aluminium oxide, contained in a vertical glass tube. Some of the constituents of the mixture pass through the column unchanged. Others are retained by the absorbent ; those with the strongest affinity for it are held near the top of the column, those with a weaker affinity lower down. The final result is that some of the substances present in the mixture become arranged in horizontal bands across the column of absorbent. (Plate XI). The latter can then be pushed out of the glass tube and the parts of it carrying different substances separated by means of a knife. The part carrying the penicillin, which is itself colourless, can be located by its antibacterial activity, using the method of assay previously described. By repetition of the process further purification can be obtained and it is possible ultimately to obtain the penicillin in the form of pure colourless crystals. In this method, too, however, considerable losses occur so that the final yield is only a small fraction of that originally present in the culture fluid. Fortunately, complete purification is unnecessary for clinical use and the process of purification need not, therefore, be carried to completion in industrial production.*

* Technical advances have, however, been so rapid that some manufacturers are supplying crystalline penicillin as a routine measure and prepare this without recourse to chromatography at all.

The chemical properties of penicillin have been the subject of intensive research both in this country and in America. Indeed it is probably true to say that no substance has ever previously been so closely investigated by so many chemists in so short a time. It is, therefore, not surprising that remarkable progress has been made. The details need not concern us here but it should be remarked that the instability of penicillin, the difficulty of obtaining working quantities of it, and certain unfamiliar features in the molecular structure, have made the investigation one of particular difficulty. It is, therefore, very satisfactory that one of the pioneer workers at Oxford, Dr. E. Chain, who initiated the chemical work and played a very constructive role in its development, has recently been awarded a share in the Nobel Prize for medicine. Among the chemists investigating penicillin, Dr. Chain is pre-eminent and certainly the most deserving of high honour. The other Nobel Prize-winners in 1946 were Professor Sir Howard Florey and Professor Sir Alexander Fleming.

The chemical investigation of penicillin has been too long and too complex to detail here. It will, however, doubtless be of interest to record the structural formula now generally accepted for penicillin I (or F) :



It may be added that four varieties of penicillin are now recognized.* In Great Britain they are known as I, II, III and K; in America as F, G, X and K. Biologically they differ somewhat in their activity against certain bacterial species ; chemically they differ slightly in the part of the molecule enclosed in brackets in the accompanying figure.

* The existence of a fifth variety of penicillin was reported in November, 1946.

The successful elucidation of the structural formula of penicillin has been followed by an attempt, in which scores of British and American chemists have collaborated, to synthesize it in the laboratory. The present position is that all the parts of the penicillin molecule have been synthesized, but it has not yet been possible to develop a satisfactory method for combining them and thus assembling the molecule in its entirety.* When this problem is solved it may be possible to carry out a synthesis economically on a commercial scale and thus avoid the vagaries of the mould and the large and costly plant necessary for producing penicillin by fermentation. While considerable progress has been made the final stages of synthesis are presenting great difficulties and it must be emphasized that synthetic penicillin is unlikely to appear on the market for several years to come. In the meantime American and British production of the natural product is increasing steadily and rapidly, and the price is falling. The present cost to the physician is about 2s. 9d. per 100,000 units.

Investigation of the biological properties of penicillin was carried out while the chemical work was progressing. Fortunately much of the work could be done with the relatively impure material available in the early stages of the work. The first task was the determination of the range of bacteria sensitive to penicillin and an investigation of its toxicity to animal tissues.

In his original work Fleming had found that bacteria as a whole fell into two main classes. Either they were relatively highly sensitive to it or they were hardly affected at all. This division corresponds quite closely to an arbitrary one made many years ago by the Danish bacteriologist Gram, who based his classification on the reaction of bacteria to certain dyes. It must be emphasized that penicillin is not a universal panacea ; even under the most favourable conditions its value is strictly limited to the range of bacteria sensitive to its action.

Among the most sensitive are the very common staphylococci and streptococci, frequently found in infected wounds, in boils, and in other local infections. They may, however,

* An account of the isolation of a minute quantity of synthetic penicillin was published in October, 1946. The method used is, however, very unproductive and of no practical importance.

also cause infections of the body as a whole. Another organism sensitive to penicillin is that causing gas gangrene. This is particularly liable to appear in wounds which have become contaminated with soil and, therefore, was of particular significance during the war. Before and during the war gas-gangrene antitoxins had been developed similar to those used for combatting other infections, such as diphtheria. Experience showed, however, that these did not give a very high degree of protection. It was found, too, that penicillin, possibly owing to the difficulty of bringing it in contact with all the organisms present in gangrenous wounds, was not as good as would be expected from its activity against laboratory cultures of the gas-gangrene organisms. The latest information, however, indicates that satisfactory results are obtained if patients in whom gas-gangrene is suspected are treated with both antitoxin and penicillin.

Other organisms particularly sensitive to the action of penicillin are those causing pneumonia, anthrax, diphtheria, and certain kinds of meningitis, syphilis, and gonorrhoea.

It has already been emphasized that some kinds of bacteria are only slightly, if at all, sensitive to penicillin. Among the most important of these are those causing typhoid fever, certain kinds of food poisoning, Malta fever, tuberculosis and plague. On the evidence at present available, penicillin is also valueless, except in so far as it prevents the development of secondary infections, for treating diseases which are caused not by bacteria but by viruses. The common cold is a typical example of this kind of disease.

In a normal, untreated infection one of the main natural defences of the body are the leucocytes of the blood. These have the power of engulfing and destroying certain kinds of bacteria. Although it is now being suspected that the importance of the leucocytes has been rather over-estimated it is nevertheless important that drugs used for combatting bacteria should not interfere with their action. Experiment showed that penicillin, at concentrations far greater than those required to destroy bacteria, is without detectable effect on the leucocytes.

Some antibacterial substances otherwise very promising lose their activity in the presence of body fluids such as blood or pus. The sulphonamides, for example, are for this reason

unsuitable for treating purulent wounds. Penicillin, however, is not affected by these conditions nor is it, like certain other drugs, less active in the presence of many bacteria than it is in the presence of a few.

All the work described above showed penicillin to be a substance whose properties gave high hope that it could be as useful in destroying bacteria within the body as those in laboratory cultures. Nevertheless, this supposition could be proved only by experiment. The earliest tests were made with mice, being animals easy to handle as well as being so small that even with the very limited quantities of penicillin available a considerable number of animals could be treated. The latter was an important consideration in assessing the value of the final results. Three sets of mice were infected with many times the lethal dose of three different kinds of deadly bacteria —*Streptococcus pyogenes*, *Staphylococcus aureus*, and *Clostridium septique*. After one or two hours half the infected animals were treated with penicillin ; the other half were left untreated to provide a check on the results. In the earliest experiments it was found that whereas all the untreated mice died, more than half the treated ones survived and were apparently none the worse for their experience. By modifying the size and frequency of the dose in the light of experience gained it was later found possible to increase the survival rate in similar experiments to nearly 100 per cent.

These animal experiments represented a great step forward, but a tremendous amount more had to be done before penicillin could be put to serious use in medicine. It had been proved that penicillin could be isolated, though in a very impure state, from the crude fluid on which the mould had been grown. It had been shown to be highly active against a range of bacteria dangerous to man. It had been shown to have a very low toxicity, permitting its introduction into the bloodstream with the object of attacking bacteria in the body. It had been shown that mice infected with penicillin-sensitive bacteria, in otherwise lethal quantities, could be saved in a high proportion of cases. Two major, and very formidable tasks remained. First it was necessary to produce sufficient penicillin to treat a number of human patients and secondly to prove that in man penicillin gave the same satisfactory

results as it gave in mice. It must be remembered that though mice are most useful for experimental work they have important physiological differences from man and furthermore are quite unable to give any account of their symptoms during treatment. Although the end-result was so satisfactory it was quite possible that in man penicillin might produce undesirable symptoms such as nausea, dizziness, or muscular pain.

Following the successful results of the animal experiments sufficient crude penicillin was laboriously accumulated at the Sir William Dunn School of Pathology to test six cases of acute sepsis. A little explanation is necessary to make clear the magnitude of this task. To obtain the necessary material some fifty gallons of crude culture fluid had to be worked up. With knowledge still incomplete, and working in a laboratory where a few cubic centimetres rather than a gallon was the normal working unit, this was no light undertaking. A very ingenious extraction plant, in which the techniques used for handling milk in bulk were successfully applied, was designed and built by Drs. A. G. Sanders and N. G. Heatley. This plant has now unfortunately been dismantled, though parts of it have been incorporated in a larger plant of a similar kind (Plate XI); this is a matter for regret as it is now of very considerable historic interest. Apart from the building of an extraction plant for dealing with considerable volumes of liquid it was necessary to make provision for growing the mould in quantity.

The necessity for avoiding contamination from the air has already been stressed. As it is difficult to keep large volumes of liquid both sterile and at the same time supplied with the air necessary for the growth of the mould, it was decided to grow it in a large number of separate containers each containing about a quart of the nutrient medium. These were set up in batches of 50 or 100. As the mould grows prolificly and produces penicillin rapidly only at temperatures well above the normal for this country—the optimum is about 75°F.—it was necessary to find some way of keeping these batches of vessels, which occupied quite a lot of space, at the correct temperature. A room, originally the dissecting theatre of the laboratory, was set aside for this purpose and fitted with shelves and automatically regulated radiators. At the height of the investiga-

tion of penicillin and other mould products this room often contained as many as 300 separate vessels.

As previously mentioned the first considerable quantity of penicillin produced at Oxford was used for the treatment of six cases of sepsis due to organisms proved sensitive to the drug. The best method of administration presented a further problem. Early work had shown that after injection penicillin is rapidly excreted in the urine so that to maintain the concentration of the drug in the blood it is necessary to give a steady supply. The most satisfactory solution has been to give the penicillin by continuous injection into a vein or by steady drip into a muscle ; the second of these alternatives seems now to be becoming increasingly important. Professor Florey has aptly likened the problem of keeping penicillin in the blood to that of keeping water in a bath with the plug out.

These first clinical tests did not prove 100 per cent successful, one reason being that the very limited supply of the drug was exhausted before treatment was in all cases complete, but the results were so promising that the decision was made to obtain substantial support from industry. With the co-operation of Imperial Chemical Industries, the first company to interest itself in large-scale penicillin production, sufficient penicillin was soon prepared to permit treatment of a further eighteen cases. Again the results were remarkable ; patients, apparently moribund, who had failed to respond to treatment of other kinds, including sulphonamide drugs, of the M & B type, were in many instances restored to health with almost miraculous speed.

From that time the reputation of penicillin was established, but there remained the huge task of solving the problem of manufacture on a really large scale, of finding the best method of administering it to the patient, and of finding the range of bacteria sufficiently sensitive to its action to justify its use.

For reasons previously mentioned industrial support was sought in the United States as well as in this country. The earliest production units were essentially larger versions of the Oxford laboratory plant. The mould was grown in a large number of separate vessels each containing only a pint or two of liquid. Two advances played a vitally important role in

making possible production of penicillin on a scale sufficient to meet all needs. One was the discovery that the mould would produce penicillin when grown throughout the bulk of the nutrient liquid instead of only on its surface. This, when all the technical difficulties were overcome, permitted the substitution of fermenters, each containing up to 20,000 gallons, for the single small vessels used in the original work. The second advance was the previously mentioned discovery that if corn steep liquor, a waste product of the milling industry, was added to the culture fluid the production of the mould was multiplied several times.

The United States is now the world's greatest manufacturer of penicillin, producing about 85 per cent of the total. World production in 1946 was about 25 million million units. Hitherto production in Great Britain has lagged chiefly because plants using the deep fermentation method have not been used. A plant of this kind is now, however, being operated by the Distillers' Company Limited at Speke, and is the largest in the world.* Some penicillin is manufactured in Canada and Australia. France has a few very small plants but while research interest is keen actual production is comparatively small. In Germany, too, the I.G. plant at Hoechst was producing penicillin at the rate of 7½ million units monthly at the end of the war, a relatively insignificant quantity, but little of this was used for clinical work, most being reserved for chemical investigation. The product was only 15 per cent pure. In this connection it may be remarked that the Germans had made very much less progress than British chemists did with material of comparable purity.

Russia, too, is keenly interested in penicillin production. Information about Russian science is always difficult to obtain, but it does not appear that they have made any important advances on British and American discoveries. It is reported that by 1947 the Soviet Union will be producing sufficient high quality penicillin to supply all its needs.

The problem of administering penicillin has already been referred to. The essence of treatment is, of course, to bring all the infecting bacteria in contact with concentrations of penicillin sufficiently high to kill them. In the case of infec-

* Glaxo, Ltd. are operating a similar plant at Barnard Castle, Durham.

tions affecting the body as a whole this can at present only be done satisfactorily by introducing it into the blood-stream, either directly by injection into a vein or by injection into a block of muscle, such as that in the buttocks.

From the patient's point of view injection is unsatisfactory, particularly if treatment is prolonged, and it would be preferable if the drug could be given by mouth. A very great deal of attention has recently been given to this problem. The main difficulty is that although penicillin is absorbed into the blood through the wall of the intestinal tract the greater part of it is destroyed by the acid contents of the stomach. Many ingenious attempts have been made to overcome this. Some workers have enclosed the penicillin in a capsule designed to carry it safely through the stomach. Others have given antacids with the penicillin to neutralize the stomach contents. It has been found, too, that there is a very great difference in the amount of penicillin destroyed when the drug is given after a fast or immediately after a meal. A factor of importance in considering oral administration is that as penicillin is not at all toxic the fear of an overdose does not arise ; apart from the question of cost it does not matter how much penicillin is destroyed provided sufficient finds its way into the blood and a therapeutically effective level can be maintained. So much progress has been made that it is very probable that a completely satisfactory method will soon be devised for giving penicillin by mouth, thus avoiding the pain and anxiety inevitable with injection.

Many kinds of infection, e.g. boils and septic wounds, are of a purely local kind and for these smaller quantities of penicillin suffice and a different method of administration is suitable. When a cavity or wound is involved a common method of treatment is to allow a steady stream of penicillin solution to drain through it. An alternative is to blow in a sterile powder containing penicillin. Penicillin-containing creams are also widely used, particularly for infections of the skin.

An important property of penicillin, and one of great social importance, is its activity against the organisms which cause venereal disease. The gonococcus, causative organism in gonorrhoea, is, in fact, one of the most sensitive of all to

penicillin. Recent work indicates that a high proportion of cases a single injection of 25,000 units effects a complete cure—virtually all cases respond to a course of treatment. Syphilis, too, especially when tackled at an early stage, is more readily cured by penicillin, and with less inconvenience to the patient, than by any other drug.

One of the most interesting of recent developments in penicillin research is the revision of original ideas of the way in which its acts. The original opinion of the Oxford workers differed from that first expressed by Fleming. The latter reported that in solutions containing penicillin bacteria were killed and totally destroyed. The Oxford workers found that bacteria were not killed by penicillin but were prevented from multiplying. They assumed that penicillin owed its therapeutic properties to this power, which would enable infection to be checked while the natural defences of the body overcame it. Paradoxically enough these apparently irreconcilable views are both correct. Penicillin is now known to destroy young, actively growing bacteria; it prevents the development of mature colonies. As most bacteria, with the exception of those in chronic infections, which have invaded the body fall into the first of the above classes, the most important therapeutic role of penicillin now appears to be the outright destruction of bacteria.

Another interesting discovery already briefly referred to (page 71) is that there are at least five forms of penicillin, differing slightly in their chemical constitution and effect on bacteria. Ordinary commercial penicillin contains a mixture of these forms, but it is possible to obtain each in a nearly pure state either by selecting special strains of the mould or by using chemical methods of separation. The difference between them from the therapeutic point of view is small but against certain bacteria the differences in their activity may soon warrant their being marketed separately.

CHAPTER EIGHT

ERGOT

THE widespread publicity given to penicillin in recent years has to some extent obscured the fact that other substances obtained from fungi are of considerable medical value. Of these one of the most important is ergot, which has been an officially sanctioned drug for more than a century. Ergot is obtained from a fungus parasitic on rye, though occasionally wheat, barley and oats are attacked. For many years preparations of ergot have been almost universally prescribed for the relief of hæmorrhage following childbirth, and more recently have proved of great value in the treatment of migraine.

Although now one of the most valuable of vegetable drugs ergot was for centuries the cause of periodic outbreaks of a disease which has taken a heavy toll of human life. Corn crops particularly rye, are liable to infection by a parasitic fungus, known to scientists as *Claviceps purpurea*. The risk of infection is always greatest after a warm, damp summer, since these are the conditions under which fungi thrive. About the time of harvest the ears of diseased rye develop long black " spurs " among the grains. These spurs are the reproductive bodies of the infecting fungus and form the ergot of modern commerce. They give the ears of rye a characteristic "smutty" appearance. During threshing the ergot is retained with the grains of rye, and in badly infected crops may amount to as much as a quarter of the total. Because of their larger size the spurs of ergot can be removed from the grain by sieving. For many centuries, however, it was not realised that ergot, when taken in large quantities, is a highly poisonous substance. For this reason districts in which the rye infection was particularly heavy were swept by outbreaks of the serious and often fatal disease which we now call ergotism. In England rye has never been grown to any considerable extent, and then mostly for fodder or for the sake of the long straw, which is particularly suitable for thatching. This country has, therefore, almost entirely escaped the ravages of ergotism. Indeed the

very word ergot is of French origin and has no English equivalent. In continental countries, however, where rye is the staple cereal, the story is very different and ergotism can rank as a national calamity at least as serious as the Black Death or Great Plague in our own history. Of European countries the highest proportion of rye bread is consumed in Poland, Germany, the Balkans, and Russia. Until quite recently France also grew large quantities of rye. As a result it is in these countries that ergotism has been the most serious menace.

The symptoms of ergotism can be of two types, the gangrenous and the convulsive. The former is characterised by a swelling of the extremities of the body, followed by a blackening and mummification of the affected part. As a result the wretched sufferers may lose hands or feet or even whole limbs. In severe cases the course of the disease may be very rapid, gangrene often setting in within twenty-four hours. The affected member may separate at a joint without pain or loss of blood. Contemporary writers tell grisly tales of epidemics of ergotism. It is related that one sufferer, a woman, was riding to hospital on an ass when she brushed against a shrub. Her leg became detached at the knee and she carried it to hospital in her arms. Boucher (Academie des Sciences 1710) tells of a patient who lost all four limbs in this way. Convulsive ergotism is characterised by more or less violent spasms of the muscles. In mild cases there is only a mild twitching of the smaller muscles giving rise to a feeling that ants are running over the skin (technically known as formication, from the Latin *Formix*, an ant). In severe cases the limbs are rigidly and agonizingly flexed. Convulsive attacks may recur for weeks or even months. Sennertus, describing a epidemic of this type, wrote in 1658 ". . . the sick would lie down, and roul up their bodies round like a Ball, or else stretch out themselves straight at length : Terrible pains accompanied this evil and great clamours and scrietchings did the sick make." In the intervals between convulsions many patients complained of a ravenous hunger. Gangrenous ergotism generally left the sufferers physical cripples, but the after-effects of the convulsive type were largely mental, characterised by mental derangement and a tendency to fits of an epileptic type. It has not yet

been definitely established why some outbreaks of the disease assume the gangrenous form and others the convulsive. Mellanby has put forward the suggestion that the convulsive type is associated with Vitamin A deficiency, but while his evidence is good, the point has not yet been conclusively proved.

Historically ergotism presents a long and fascinating story. It is doubtful whether the disease was known to the Greeks and Romans, largely because little rye was grown round the Mediterranean. In the Middle Ages, however, there are many authentic references to serious epidemics, particularly in France. The records of the time call the disease by various names, such as the Holy Fire (sacer ignis), Divine Wrath and Fire of St. Anthony, but the description of the symptoms leave no doubt that all these referred to ergotism. The earliest known outbreak occurred in 857, at Xanten in Westphalia, but there is no doubt that rye-eating communities have suffered since long before the time of extant written records. In this first account it is stated that " . . . a great plague of swollen blisters consumed the people by a loathsome rot, so that their limbs were loosened and fell off before death." In 945 the disease appeared in Paris. Many of the sufferers turned to the church of St. Mary for succour, and were there fed by Duke Hugh, Count of Paris. These people were saved, though " backsliders " who returned to their own homes suffered a relapse. Clearly Duke Hugh had supplies of sound grain. In 994 a violent outbreak occurred in Aquitane and over 40,000 people died. The terror of the time was increased by the approach of the millenium, when the world was expected to end. At that time the only form of treatment was sprinkling with holy water and the sight of the bones of St. Martial, disintered for the purpose. An outbreak of 1039 was attributed to divine wrath at the breaking of the celebrated " truce of God " which among other provisions, restricted fighting to Mondays, Tuesdays and Wednesdays. This outbreak in Lorraine was clearly of the convulsive and gangrenous type " . . . many were tortured and twisted by contraction of the nerves: others died miserably, their limbs . . . blackened like charcoal."

The seriousness of epidemics of ergotism on the Continent is shown by the fact that the Order of St. Anthony founded

several houses for the specific purpose of caring for sufferers. It is said that mummified cast-off limbs were still preserved in the Abbey of St. Anthony, at Vienne, in Dauphiné, as recently as 1702. The foundation of these houses explains also the association of the disease with the name of St. Anthony.

Further great outbreaks of the disease have been described by many writers up to the present time. A big outbreak occurred in Brittany in 1347 and in Saxony in 1486. In the marshy Sologne area of France, where much rye was grown, many outbreaks are recorded. In 1581 an outbreak in the Duchy of Luneburg, near Hamburg, caused 123 deaths in two villages alone. Further records show that the disease caused many deaths every year, but that widespread epidemics occurred at irregular intervals, determined chiefly by climatic conditions favourable to a particularly heavy infection of the rye. In 1770–1771 an unusually severe outbreak occurred all over Europe, and was followed by another in 1777, when 8,000 people are known to have died in the Sologne area alone. As recently as 1926 there was an extensive outbreak in Russia, and more than 11,000 cases became known to the authorities.

It has already been stated that England has largely escaped this scourge, owing to the negligible consumption of rye. In the only recorded outbreak of gangrenous ergotism, occurring near Wattisham in 1762, the cause was eventually found to be infected wheat, a very rarely observed condition. The outbreak was very small, and confined to a single family. There was, however, a considerable outbreak of the convulsive type in Manchester as recently as 1928. This occurred among Jewish refugees from Central Europe and altogether 200 persons were affected, though none very seriously. Investigation showed that, following their national customs, the immigrants had been consuming rye bread, prepared from rye grown in South Yorkshire. Examination of this crop showed that it contained 1 per cent of ergot. In this country we must, therefore, consider ourselves very fortunate in escaping a disease which has played such havoc in other parts of Europe.

It is remarkable that thousands of lives were lost through ergotism for centuries after the true cause of the disease was known. Dodart, writing to the French Academy of Sciences in 1676, showed quite clearly that he recognized the connection

between ergotism (as it is now called) and the consumption of infected rye. This view was accepted in educated circles in France and never contested. In other parts of Europe, however, this fact was either ignored or disputed until the beginning of the nineteenth century. Even in France this essential piece of knowledge was apparently not used as a means of checking outbreaks of the disease, and it was not until the great European outbreaks of 1770 and 1777 that any legislation was introduced. The Hessian government for example, in 1770, issued orders that ergotised grain must be cleaned by sifting, and detailed punishments for neglecting to do so. Other European governments issued similar regulations, but at the present time these appear to have lapsed and the sale of ergotised rye is now apparently controlled only by general regulations relating to the sale of poisonous foodstuffs. In the U.S.S.R. regulations made after the 1926 outbreak fix the upper limit of ergot in rye flour as 0.15 per cent. In spite of regulations, however, many deaths still occur from ergotism, particularly in the Balkans and Russia. Under war-time and post-war conditions the problem is likely to be far more serious. The chief difficulty lies apparently in the obstinacy of the peasants, who will not be persuaded of the danger of ergotised grain until they have discovered it by bitter experience. It is related that in order to prove its harmlessness a peasant near Perm consumed a glass full of ergot : he died on the following day.

The history of ergot is black in more ways than one, but in spite of its evil reputation modern medical science has been able to turn its remarkable properties to good use. Chemical analysis has shown that the main active principles of ergot are ergotinine, ergotoxine, ergotamine and histamine. Occasionally these substances, or combinations of them, are used in the pure state, but more commonly extracts of ergot itself are used, prepared under carefully defined conditions laid down by the pharmacopœias of different countries. A few statements have been made that these preparations can lead to outbreaks of gangrene, but a careful review of many alleged cases has shown that when the drug is used in the quantities and manner prescribed the gangrene can be attributed to sepsis and not to the drug itself. Ergot preparations are now almost universally

used for the control of hæmorrhage after childbirth, and for this purpose it is the most useful drug known to medicine, saving many lives every year. More recently it has been shown to have a strong effect in the relief of migraine : attacks which would normally last a full twenty-four hours commonly resolve themselves in one hour. When used under proper supervision ergot's potentialities for good far exceed its old power for evil. It is interesting to observe that although in Europe ergot is a comparatively modern drug, its value in midwifery has, in fact, been known elsewhere for centuries. The Chinese in particular used it for this purpose at a very early date, and its valuable properties were certainly known to the famous Moorish physician Avicenna (980–1036). Had this knowledge spread to Europe a vast amount of suffering and death might have been avoided.

So great is the modern demand for ergot for medical purposes that it has become an important article of commerce. At present the annual demand is of the order of 250 tons, but precise data is not available. In normal times the two most important sources of supply are Eastern Europe (Russia and Poland) and the north-western corner of the Iberian Peninsula, including parts of Spain and Portugal, where the growth of ergot is favoured by the warm damp climate. Until recently sufficient ergot could be obtained from naturally infected rye crops, but during the last few years increasing difficulty has been experienced in making the supply equal the demand. Two main factors have contributed to this state of affairs. From the long-term point of view the most important is the fact that steadily improving methods of agriculture are reducing the incidence of infection in crops, and this in the face of an increasing demand. Secondly, the outbreak of war temporarily cut off all important sources of supply except Spain and Portugal, and it takes time to restore trade relations. Even before the war experiment was proceeding to produce ergot on a large scale by deliberately infecting crops of rye, but it is difficult to estimate the commercial value of this work. It appears that a yield of about 500lb. of ergot can be obtained per acre.* The price of ergot varies enormously from year to

* During the war ergot was produced artificially in India, but it is doubtful whether this would be profitable in normal times.

year, according to the local climatic conditions on which depends the heaviness with which the crops are infected. The average price is about three shillings per pound, but in 1919 the price of Russian ergot was twenty shillings per pound, while in 1930 it was less than one shilling. Crude Spanish ergot is generally packed in bags of 75 kilos weight, Eastern in bags of 50 kilos. It is interesting to observe that the bags of ergot are often heavily attacked by mites upon which the ergot, so deadly to humans, is apparently without effect. The high price fetched by good quality ergot has even led to the appearance of a new type of criminal. These ingenious, if misguided, men make ergot " forgeries " from dough blackened to resemble the natural product by addition of earth or charcoal.

CHAPTER NINE

OPIUM

OPIUM, the dried juice or latex from the seed capsules of the opium poppy, is at the same time among the oldest and the most valuable drugs known to medicine. Indeed, to the famous physician Sydenham, is attributed the aphorism that "few would be willing to practise medicine without opium."

There is no doubt that knowledge of the properties of opium is of very great antiquity. Morpheus, the god of sleep who eventually gave his name to morphine, the active principle of opium, was commonly represented as a fat, winged child bearing a vase in one hand and a bunch of poppies in the other. The following passage in Homer's *Odyssey* (Bk. IV, line 294 of Chapman's translation) is generally considered to refer to the drug.

But Helen now on new device did stand,
Infusing straight a medicine to their wine
That, drowning cares and anger, did decline
All thought of ill. Who drunk her cup could shed
All that day not a tear, no not if dead
That day his mother or his father were,
Not if his brother, child, or chiefest dear
He should see murder'd then before his face.
Of what was good, would Helen ever have.
And this juice to her Polydamna gave,
The wife of Thoön, an Egyptian born,
Whose rich earth herbs of medicine do adorn
In great abundance.

The reference to Egypt as the source of this and other drugs is an interesting one, and quite in accordance with modern knowledge of Egyptian medicine.

Homer's references do not prove that in his time the pain-killing properties of opium were known, though it is very probable that this was so; he refers rather to its power of dispelling care and promoting sleep. This property was, how-

ever, well known to the Assyrians as the following prescription for an opium suppository shows :

> . . . if a man's belly unexpectedly is irritated . . . and while it hurts him he cries out . . . thou shalt reduce lion-skin, mix with lion fat (opium) ; let it dry again, mix with cedar oil, make into a suppository and put it on his anus.

It may be mentioned that very similarly compounded opium suppositories are used to-day. This method of administration has the great advantage that absorption into the body takes place slowly.

In succeeding centuries the use of opium, both as a medicinal drug and as a drug to cause pleasurable sensations, has become widespread. In its latter role it now constitutes a national vice in many parts of the world, and it is grown widely in South East Europe, Asia Minor, Persia, India and China. Modern medicinal opium is now obtained largely from Asia Minor.

By the eighteenth century opium was well known throughout Europe. Pitton de Tournefort in his *Materia Medica*, translated into English in 1798, gives an interesting account of its medical use in his day and some amusing tales of its use as a drug of addiction among oriental people. He distinguishes carefully between the " hypnotick," or sleep-producing properties, and the " narcotick " or pain-reducing qualities of opium. He mentioned, too, that the active principle lies in the seed case, and not in the seeds, of the poppy and says that in France, Italy and elsewhere poppy seeds are used in confectionery without harmful results. His account of the production of opium in Turkey is as follows :

> " The Turks use to sow whole Fields with Poppy-seeds, as we do with Wheat ; and when the Poppies come to perfection, they make some slight incisions into the Heads, out of the which wounds instantly issue some white drops, like Milk, which afterwards thickening or concreting, they call Opium."

He describes, too, the preparation of tincture of opium ; " Liquid Laudanum is made by dissolving Opium in Spirit of Wine." He ascribes to the drug, however, considerably more

therapeutic properties than would be admitted to-day, writing thus :

> " The use of Opium and Laudanum is very proper, seasonable and beneficial in all Fluxes of the Belly, Catarrhs, Hæmorrhages, Distempers of the Breast, and others of that kind, the Body being first purged according to Art, and as Necessity requires."

De Tournefort was also evidently well acquainted with the after-effects of opium for he writes :

> " . . . a comatose or sleepy Distemper sometimes ensues upon the unseasonable use of Narcotick Medicines ; . . . some, after the taking of Opium, are apt to complain of a grievous pain in their Head."

Finally he refers to opium as a drug of addiction, being commonly used both as a stimulant and as an aphrodisiac, as the following quaint passages reveal :

> " . . . Turks, who commonly devour a large quantity of Opium when they are going to engage in a Battel, to make them bold and couragious."

> " . . . that there is an Electuary prepar'd by the Indians of Opium, which the Chinese make use of to excite venery ; by the use whereof they are so enraged with a libidinous Fury that the Whores are not able to endure their furious assaults and encounter."

An account by a Dr. Edward Smyth in the Philosophical Transactions of the Royal Society for 1695 also shows that the habit of opium eating was well established at the time in Eastern Europe and Turkey. Smyth, on a visit to Smyrna, sought out the most famous of local opium-eaters, Mustapha Shatow. The latter told him that he was in the habit of taking three drams of crude opium daily—half in the morning and half in the afternoon—though he claimed with pride that he could safely take twice this quantity. He records the stimulating, yet habit-forming qualities of the drug in the following words :

> " It always has the same effects, giving him Vigour and Spirit, and is now become as necessary to him, as any other part of his Sustenance ; that it makes him fitter for

procreation, for he has many Wives and Children . . . that the want of it and the desire of taking more grows daily upon him."

George Young, an Edinburgh doctor—*A Treatise on Opium*, 1753—emphasized the value of opium in treating coughs, from which he himself suffered severely. It is now well established that morphine, the main active principle of opium, exerts a considerable depressing effect on the cough centre of the brain. Young gives an interesting account of the effects of an exceptionally large dose of laudanum, which he found :

> " . . . brought on a great hoarseness, with a noise in my ears and a giddiness and confusion of my head. I fell asleep, but soon waked again, with violent startings and confusion, attended with a sense of faintness or failing about the heart, that seized me as often as I was dropping asleep."

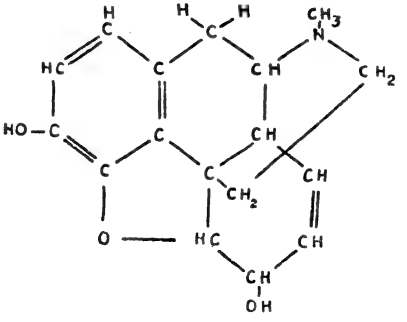
Dover's Powder, another old remedy which is still in use to-day, is a combination of opium and ipecacuanha and is valuable for the treatment of persistent, dry coughs.

By the late eighteenth century the valuable medicinal properties of opium, both as a hypnotic and a narcotic drug, were fairly generally recognized and attempts began to be made at chemical investigation with the object of isolating the active principle. One of the first attempts was probably that of Geoffroy in the first half of the eighteenth century. He reached the conclusion that " the soporific quality was owing to its sulphur," but does not appear to have described his sulphurous principle or to have compared its qualities with those of the original opium. Even before the time of Geoffroy, in the seventeenth century, certain concentrates of opium were sold under the title *Magisterium Opii*, but the preparation of these can scarcely rank as a proper chemical investigation.

The first really important results of chemical work came in the first years of the nineteenth century, when Bucholz tried to obtain a crystalline salt to use in the place of opium. About the same time Derosne, an apothecary of Paris, obtained crystalline material by diluting a syrupy aqueous extract of opium. This was probably a mixture of two of the main opium alkaloids, morphine and narcotine. In 1804 Seguin read a

paper entitled " Sur L'Opium " to the Institute of France, describing morphine which he isolated in the form of colourless crystals. Unfortunately Seguin's results were not published until ten years later and in the interval Sertürner completed an independent investigation and published his results. Although Seguin has the prior claim in the actual isolation of morphine, Sertürner's chemical investigation was very much more thorough. He recognized morphine as a " vegetable alkali " or alkaloid (page 31) and isolated also the organic acid, meconic acid, with which it is combined in raw opium. Liebig, the famous German chemist, investigated morphine in 1831 and assigned it an empirical formula of $C_{34}H_{36}O_6N_2$. Sixteen years later Laurent showed that Liebig's was a double formula and that the correct one was $C_{17}H_{19}O_3N$.

The elucidation of the precise arrangement of the atoms in the morphine molecule has challenged the skill of organic chemists for a century, but even today the challenge has not been fully met. Some of the fine points in the chemical structure have not yet been finally established, and although large fragments of the molecule have been synthesized, a total synthesis has not yet been achieved. The structural formula proposed by Robinson and Gulland is as follows :



The action of opium on man is due almost entirely to its morphine content, which is about 7 to 15 per cent by weight. Opium contains also more than thirty other related alkaloids, some of which, such as codeine, are used in medicine. A few of these will be discussed later.

The advantages of using the pure active principles of drugs, rather than the raw material with its variable physiological effects, was stressed in the introductory chapters of this book and it is, therefore, not surprising that pure morphine is produced commercially in considerable quantities. The modern method of preparation is essentially as follows : Raw opium is extracted with a solution of calcium chloride, which precipitates meconic acid (page 91) and certain other impurities as insoluble calcium salts. The resulting solution is concentrated by evaporating the water and two of the other opium alkaloids—narcotine and papaverine—are removed by the cautious addition of sodium acetate. When the remaining solution is made slightly alkaline by the addition of soda crude morphine is precipitated and is filtered off. This crude material is neutralized with hydrochloric acid and purified by repeated crystallisation from hot water. This final material still contains codeine which can be extracted with benzene or ether, in which it is only slightly soluble. For medical purposes morphine is generally used as it salts with hydrochloric, sulphuric, tartaric, or acetic acid, since these are much more soluble in water than morphine itself.

It is often said that opium, or its active principle morphine, is at once among the greatest blessings and the greatest evils of mankind. Yet probably on balance the good it does in relieving the suffering of otherwise unbearable pain outweighs the damage, widespread though it is, which results from addiction to the drug. The latter is a problem which will be discussed later. The most important role of morphine in medicine is for the relief of pain. Its use in this respect is, however, complicated by the ease with which habituation is established—many opium and morphine addicts have attributed their downfall, rightly or wrongly, to incautious medical use. The use of morphine is, however, indicated in pain arising in two kinds of circumstance. It is most valuable for giving relief of pain and rest to a patient in whom the cause of severe pain is transient and will respond to treatment. Morphine can also be satisfactorily used to give relief to sufferers from incurable and painful diseases such as cancer. The great value of the drug is that it not only deadens pain but also acts as a soporific. For the relief of pain an average dose is about $\frac{1}{4}$ grain

but sometimes twice as much is necessary. Very large doses must, however, be avoided as they may cause symptoms similar to those of shock and may prove fatal to severely injured men. Morphine and opium must also be avoided in the case of infants, who are particularly sensitive to it, and used with great care in the case of old people. In all cases it is desirable, except in cases of very great urgency, to start with a small dose as there is always the possibility of an unsuspected personal idiosyncrasy which may cause a severe reaction to quite a moderate dose.

Morphine may be administered in various ways. Morphine ointments are sometimes used in the erroneous belief that the drug has an analgesic effect on the peripheral nerve endings. The only satisfactory method of external application is as a rectal suppository ; the use of this by the Assyrians was mentioned earlier in this chapter. The drug can also be given by mouth but if, as often is the case, a very quick response is wanted, the best method is by injection under the skin.

Opium and morphine produce certain effects, other than hypnosis and the relief of pain, which are also made use of in medicine. Its use causes constipation and it is, therefore, a valuable method for checking diarrhoea. As it diminishes peristalsis, the natural rhythmic movement of the intestines, it is used to treat cases of appendicitis where operation is impossible or impracticable. It is used, too, to control hæmorrhage, and particularly intestinal hæmorrhage, because it reduces both voluntary and involuntary movements. The restlessness of madness is, however, best treated by hyoscine, a drug derived from henbane.

Morphine has also a depressing action on the nervous centre involved in the action of coughing, and it is, therefore, often used with great benefit in giving relief and rest in cases of painful and intractable coughs. Its use in the nineteenth century for this purpose has already been referred to. Codeine, which is chemically a methyl ether of morphine and is also found in opium, is also widely used for this purpose. Codeine has the advantage that while it has a quarter of the effect of morphine on the respiratory centre it is ten times less powerful as a narcotic.

Acute poisoning by opium or morphine, as distinct from the chronic poisoning of addiction, is not uncommon. It may result from errors in treatment, or from deliberate attempts at suicide or murder. The main symptoms are slow and deep breathing, due to the action on the respiratory centre, the onset of coma and the pin-point contraction of the pupils of the eyes. Death eventually takes place from asphyxia due to the interference with breathing. Atropine—the active principle of belladonna—is used as an antidote as this substance has an opposite, stimulating, effect on the respiratory centre.

The use of opium as a drug of addiction is, and has been for centuries, a most widespread evil. For this purpose it is either eaten or smoked ; the former method is much the older of the two. There is apparently little difference in the physiological effects produced by the two methods. The first effect of the drug is said to be a stimulation of the intellectual powers, though this is accompanied by a diminution in the powers of concentration. At the same time the imagination is powerfully excited, the addict feels himself to be master of the world and travels through a dreamland where all his desires are fulfilled. Eventually sleep, broken by bizarre and fantastic dreams, overcomes him. It seems, however, that the effects on Western peoples is somewhat different from that on those of the East. The dreamy effects are less pronounced and the stimulation of mental capacity more marked. Among Eastern races, too, use of opium causes apparently more physical excitement, sometimes progressing into delirium, than it does among the people of the West.

The use of opium, as of other narcotic drugs, is essentially a result of the urge to escape, if only for a brief time, from the cares and troubles of daily life. Unfortunately this is not the only effect of the drug. As with tobacco, only to a far more marked extent, a craving is soon established. Increased doses are necessary to obtain the same effects and the continued use of the drug is attended by physical and mental deterioration. The life of the confirmed addict centres round the drug and he will eventually resort to the meanest devices in attempts to obtain it. The addict may resolve to give it up, but at the same time, such is the craving, resorts to lies, deceit, bribery, and even violence, to obtain more. The only method of cure, and too

often it is followed by relapse, is institutional treatment. It is generally, but not universally, agreed that the best method of effecting a cure is to cut off all supplies of the drug immediately, rather than to attempt to lessen the distress of the patient by doing so gradually by slowly diminishing the daily dose. The patient so treated is subject to all kinds of distress. He sweats profusely, his appetite fails, he suffers from shortness of breath, his head aches, his skin itches almost intolerably. Mental symptoms are equally unpleasant; the addict is subject to the most extraordinary hallucinations. He is possessed with a deadly fear, spectres arise from the grave to torment him, strange monsters threaten him on every side. From time to time the horror is increased by fits of violent delirium. These symptoms may persist for as long as a week, but at the end of that time the patient begins to return to normal. In another week or so the cure is complete. Only too often, however, it is of short duration and the patient once again falls a victim to the fatal fascination of the drug.

Attempts have been made to relieve the distress of the patient by putting him to sleep during the early stages of the period of deprivation. For this purpose the induction of coma by means of insulin—a form of treatment also used for certain kinds of insanity—has had some popularity. About 1880 cocaine was introduced as a means of tiding the patient over the most difficult initial stages of cure. Unfortunately this only introduced a second evil—cocaine addiction—which has kept a strong grip ever since.

The opium addict takes the drug either by mouth or by smoking—the latter is probably the most popular at the moment, but the former is certainly the older method of administration. It is generally regarded as essentially a vice largely confined to the Middle and Far East. This is by no means wholly true. Before the last war it was estimated that in the United States about 700,000 pounds of opium was consumed annually—about ten times the quantity needed for bona fide medical purposes. In Europe opium consumption is low compared with that in the United States, Asia, and parts of Africa, but there is a relatively high consumption of morphine, the active principle of the drug.

It is not generally realized that opium eating was a very common vice in England a little over a century ago. In all the great cities of the country the counters of the apothecaries' shops displayed quantities of opium pills. Opium was cheaper and more plentiful than alcoholic drinks. Life insurance companies included a saving clause relating to opium-eating in their policies and considerable litigation arose from disputes over payment.

In his book *Confessions of an English Opium Eater* (1822) Thomas de Quincey gives an excellent account of the prevalence of the vice in England and of his own suffering from his subjection to it. He gives a vivid account of the hallucinations he suffers, his fits of melancholy, the ruination of his health, and his agonized attempts to break himself of the habit. It is of interest that he first took opium, on the advice of a friend, to relieve the severe pain of toothache. Despite his lifelong addiction to the habit de Quincey lived to the good age of 73. He regarded his avoidance of the worst effects as being due to his own considerable will power, which enabled him to confine himself to a moderate daily dose, and to his habit of taking as much exercise in the fresh air as he could.

Opium eating has still, it is said, left an evil legacy in the habit of mothers in the slums giving squalling children opium preparations to quieten them.

Opium smoking is most prevalent in Asia, but it is not unknown in Europe and America, where it is found chiefly among foreign seamen and their associates. The opium pipe, sometimes richly ornamented, is generally about eighteen inches long. The bowl of the pipe is detachable and is inserted into the stem about six inches from its end. The other necessities for opium smoking are a burning lamp and a needle. The needle is heated and dipped into the crude opium, causing it to melt into beads which stick to the hot metal. The smoker rolls the beads together in a small pellet and finally, after further heating and rolling, carefully introduces it by means of the needle into the bowl of the pipe. The withdrawal of the needle leaves a channel connecting with the stem of the pipe. The opium is then lit and the smoker puffs vigorously, prodding and relighting the opium from time to time in order to keep the pipe going.

In fiction opium smoking dens are often represented as palaces of luxury. Most frequently, however, they are squalid in the extreme ; one reason being, no doubt, that while under the influence of the drug the addict is scarcely aware of his surroundings.

In January, 1946, an opium den was raided in the West End of London and six Chinese subsequently appeared in court and were fined, though the penalties were surprisingly light. The proprietor was fined £10 and his clients £2 or £3 a piece. The following description of the premises was given in the *Evening Standard*.

> " When the door was opened opium fumes came through. Inside were found four men lying on a blanket-covered bench with a lighted lamp beside them. Cheng (the proprietor) was lying on a mattress on the floor smoking opium. Searching the place, three lighted lamps, two opium pipes, and seven packets of opium were found. Underneath a bench was a block of opium and a tin of opium residue."

The pipes, lamps, stands, and opium were displayed at the Marlborough-street Police Court.

In Batavian opium dens, probably typical of the East, the accommodation is generally spartan. The smoker is provided with a pipe, a needle, and a lamp ; he has also a mat spread on the floor and a wooden pillow for his head. Sometimes cups of tea and ordinary cigarettes are also provided. Incidentally, Professor Thoms, of Berlin, in an account written before the last war, throws interesting light on the economics of Batavian opium dens. He reported that the smoker was expected to keep the scraps of opium left in his pipe—corresponding to the " dottle " in an ordinary pipe—and to give them to the proprietor on leaving. The latter sold them back to the opium factory where they were purified and re-sold to addicts. This payment represented the proprietors sole source of income ; his clientèle made him no other payment.

Although the effects of opium are in the main due to the morphine contained in it, the raw drug contains also certain other important alkaloids. The presence of papaverine in opium renders the latter less constipating than morphine alone. Of the other alkaloids codeine (which chemically is the methyl

ether of morphine) is the most important. Its properties are in the main similar to those of morphine. It is often prescribed for treating persistent coughs because it is a less dangerous drug than morphine. In recent years tablets containing a mixture of aspirin, phenacetin and codeine have been sold without restriction in chemist's shops. They are in considerable demand for self-medication for neuralgic pains ; women in particular favour them for the relief of pain during menstruation. It should, however, be remarked that this method of sale is not free from objection. Codeine, though much less powerful a drug than morphine, is nevertheless dangerous and is liable to result in habituation. Codeine addicts are rare, but it seems undesirable to make such a drug available in any form without prescription. The symptoms of addiction are similar to those which result from indulgence in morphine or opium.

Heroin is another important derivative of morphine. Chemically it is the hydrochloride of diacetylmorphine. Its general physiological effects are similar to those of morphine, but while it occupies an important place in modern medicine, being used also for relieving cough, it, too, has the great disadvantage of being habit forming and wreaking great mental and physical devastation. It is said that the effects of heroin are more prolonged than those of morphine and, once contracted, the habit of addiction is even harder to break. The illegal consumption of heroin is comparable with that of morphine ; many addicts take both drugs.

CHAPTER TEN

COCAINE

THE history of cocaine bears certain resemblance to that of quinine. Like the latter it was first introduced from the New World ; the drug is derived from the leaves of a shrub, belonging to the botanical genus *Erythroxylon*, which grows wild in Peru and elsewhere in South America. There the leaves have for long been habitually chewed by the natives for the sake of their mentally and physically stimulating properties. Cocaine was not, however, used in medicine, where it is of great value because of its power of producing local anæsthesia, until the latter half of the nineteenth century. Thereafter the greatly increased demand for the drug made the wild plant insufficient to meet the demand and, as in the case of quinine, extensive plantations were established in Java, whence came the greater part of the world's supply in the years immediately before the last war. Unfortunately increased knowledge of the medical value of cocaine has resulted in large quantities being used as a drug of addiction. The effects of this abuse of the pure drug have been very much more serious than those produced upon South American natives by chewing the leaves, which contain only small quantities of cocaine.

Although the tobacco plant grows wild in Peru the natives have not, until quite recently, used this herb for anything but medicinal purposes. Indeed it is interesting to reflect that on its first introduction into Europe far greater importance was attached to tobacco as a medicine than as a stimulant. Jean Nicot, French Ambassador to the Court of Lisbon in 1559, reported that preparations of tobacco had a remarkable curative effect on boils and ulcers. Soon tobacco came to be regarded as a universal panacea throughout Europe, and though the claims made for it are no longer recognized the work of Nicot was commemorated in the eighteenth century, three hundred years after his death, by giving the name " nicotine " to the active principle of tobacco.

The Peruvians, however, made up for their abstinence in this respect by their national habit of chewing coca leaves, a habit which has for centuries been almost universal among the natives of South America. For chewing, the leaves are smeared with a little lime, and then rolled. It is very interesting that modern science has shown that the effect of this addition of lime, discovered empirically centuries ago, is to release the cocaine from substances with which it is combined. Today, preliminary treatment of the leaves with lime or other mild alkali is an essential step in the commercial production of cocaine.

Coca, as it is called, is sold in all the native markets of South America and is one of the most eagerly sought of all the products displayed. Coca chewers vary considerably in the quantity they take. A moderate ration would be about one ounce daily and this is said to produce no worse effects than those which result from moderate smoking of tobacco. Confirmed addicts, however, will take ten or twelve times this quantity and in them symptoms comparable with those found in cocaine-addicts make their appearance.

The following passage from Prescott's *Conquest of Peru* gives an excellent account of the coca-chewing habit :

> " They have found a substitute for its (tobacco's) narcotic qualities in the coca (*Erythroxylum peruvianum*) or *cuca*, as it is called by the natives. This is a shrub which grows to the height of a man. The leaves when gathered are dried in the sun, and, being mixed with a little lime, form a preparation for chewing, much like the betel-leaf of the East. With a small supply of this *cuca* in his pouch, and a handful of roasted maize, the Peruvian Indian of our time performs his wearisome journeys, day after day, without fatigue, or, at least without complaint. Even food the most invigorating is less grateful to him than his loved narcotic. Under the Incas, it is said to have been exclusively reserved for the noble orders. If so, the people gained one luxury by the Conquest ; and, after that period, it was so extensively used by them that this article constituted a most important item of the colonial revenue of Spain. Yet, with the soothing charms of an opiate, this weed, so much vaunted by the natives, when used to excess,

is said to be attended with all the mischievous effects of habitual intoxication."

In a footnote to the above, Prescott quotes a contemporary traveller, Poepigg, as describing the effects of habitual use of *cuca* as very similar to those produced on the chewer of opium.

Modern evidence supports Prescott's statement. Moderate indulgence in coca-chewing probably produces no ill effects and indeed is of real value to the Indians in performing the hard tasks—to carry a two hundred pound sack for miles along stoney mountain tracks is nothing out of the way—of their daily life. Over-indulgence, however, as with tobacco and other narcotics, may produce symptoms of serious poisoning marked by mental and physical deterioration.

The serious scientific investigation of coca leaves dates from the second half of the nineteenth century. But for a chance the credit for the discovery of the properties of cocaine would, as he records in his autobiography, have gone to Sigismund Freud, the founder of modern psychology. In 1884, he was investigating cocaine, about which little was then known. It had been named by Niemann in 1860, who had isolated it from coca leaves, and it had been found to numb the tongue and lips. Textbooks of physiology recorded briefly that cocaine produced profound effects on the central nervous system. Yet no one had seen the immense possibilities inherent in these qualities. In 1882 Dr. Karl Koller and Dr. Sigismund Freud were working in Professor Stricker's laboratory in Vienna. Koller was looking for a substance which would produce local anæsthesia, particularly for operations on the eye, where consciousness and co-operation by the patient is very desirable. The substances Koller tested all proved unsatisfactory and, discouraged, he gave up the search, though he kept a close watch for reports of new substances which might serve his purpose.

Meanwhile Freud was trying to treat morphine addiction (see chapter on opium) by substituting cocaine for morphine. Ultimately this kind of treatment proved disastrous, replacing a bad addiction by a worse one. At the conclusion of this work he decided to investigate other properties of cocaine, and in particular its anæsthetic effects on diseased eyes. At the crucial moment, however, he had the opportunity for a holiday, and

decided to visit his fiancée in Hamburg—yet another example of the far-reaching effects of love. Before leaving he suggested to a friend of his, an oculist named Königstein, that he should carry out the decisive ocular experiments. For some reason Königstein handed this work on to Koller and it thus fell to the latter to make the very important discovery of the remarkable local anæsthetic properties of cocaine. He communicated his results to the German Ophthalmological Society on September 15th, 1884. In his autobiography Freud records that he bore his wife no ill-will for her innocent role in robbing him of this discovery. Certainly he earned ample fame later in quite another field of science.

To the oculists and their patients cocaine came as a great blessing. No organ is more sensitive than the eye, and without local anæsthesia the surgeon's work is made very difficult owing to involuntary reflex movements at the lightest touch. Merely by running into the eye a few drops of a solution of cocaine this difficulty can be overcome. Very soon surgeons specialising in operations on the throat and larynx realized the value of cocaine and used it extensively. A New York dentist, Halstead, showed that teeth could be painlessly extracted by injecting cocaine into the nerves serving them.

In a few years cocaine became firmly established as an aid to all kinds of small surgical operations, and attempts were made to extend its use to more important operations. One of the first of these attempts ended disastrously. A doctor named Kolomin successfully excised an intestinal abscess under cocaine anæsthesia. Unfortunately the patient died, primarily from poisoning due to the very large dose of cocaine which proved necessary, and Kolomin committed suicide. Soon afterwards, however, Karl Schleich showed how this difficulty could be overcome. His technique was to use a much weaker solution of cocaine than was then customary and to use this to infiltrate the whole region affected by the operation. Anæsthesia results both from the action of the cocaine and from the local anæmia caused by the injection of the liquid. Today, cocaine, or various synthetic substitutes which will be described later, can be satisfactorily used even for major operations and in such cases general narcosis is not necessary.

The demand for cocaine is so great that its production is an important industry. Some is still obtained from leaves gathered in South America, but before the war the bulk came from plantations established in Java. At the time of writing there is no information as to how these fared during the Japanese occupation. The cutting off of supplies from Java was less serious than might have been expected, because a number of synthetic substances were available which will produce effects very similar to those of cocaine. There is, nevertheless, still a considerable demand for cocaine itself, particularly for operations of the eye, as the substitutes, though in some ways actually superior to cocaine, are in some other respects less satisfactory.

Three species of the coca plant are commonly used for preparing the drug on a commercial scale. They are *Erythroxylon coca, E. Carthagense* and *E. Truxillense* respectively. From Java leaves the drug is obtained largely in the form of cinnamyl cocaine, from which cocaine itself can be prepared by further treatment. The dried powdered leaves are treated with lime, soda or other dilute alkali to release the cocaine (cf. page 100). The mixture is then extracted with petrol. As petrol does not mix with water the solution of crude cocaine in petrol can easily be separated from the watery residue of the leaves. If the petrol solution is shaken with dilute hydrochloric acid the cocaine, which is an alkaloid or " vegetable alkali," passes into the watery layer which can then be separated from the petrol.* The latter can then be used to extract a fresh lot of coca leaves. The acid solution is concentrated when, as they are only sparingly soluble, salts of the alkaloids with hydrochloric acid separate out and can be further purified by recrystallisation. In the case of South American coca leaves the precipitate consists mainly of cocaine, but when Java leaves are used the precipitate consists largely of cinnamyl cocaine. This difference is due to differences in the kind of plant and way of growing it. Cinnamyl cocaine is converted into cocaine in the following way. The precipitate is boiled with dilute acid for an

* Contrast penicillin (page 69) which is also purified by partition between two immiscible solvents but which, as an acid and not an " alkali," distributes itself in the opposite direction, passing into water which is weakly alkaline.

hour, when the cinnamyl cocaine is converted into methyl alcohol (wood spirit), cinnamic acid, and a substance called ecgonine. The latter crystallises out of the solution and can be removed. It is mixed with a little soda and the mixture is extracted with alcohol. On evaporating the alcohol a residue of pure ecgonine is left. This substance contains almost all the elements of cocaine, but to convert it into the latter two small groups of atoms must be added to it. This can be done by simple chemical processes. Chemically cocaine is benzoyl ecgonine methyl ester, and its structural formula is given on page 32.

Cocaine fulfills most of the requirements for a local anæsthetic for general medical use. It has a specific action on the endings of sensory nerves and exerts this action immediately, without preliminary stimulation or irritation. Many substances otherwise suitable as local anæsthetics fail because they cause pain before they cause anæsthesia. The anæsthesia lasts for some hours, the precise time depending, of course, on the quantity used. Cocaine has no effect on adrenaline and the two can be injected simultaneously. Adrenaline is a hormone which was first isolated from the adrenals (organs near the kidneys), but is now available synthetically. It has the remarkable property of contracting blood vessels very strongly—it is called a *vaso-constrictor*—and when administered with a drug such as cocaine has, therefore, the power of localising its action by greatly reducing the quantity which is carried away by the blood.

Although cocaine is very satisfactory in all the above respects it has two serious disadvantages. In the first place it has a powerful toxic effect on the central nervous system. This can to some extent be off-set by using adrenaline to localise the drug. Even more serious, however, is the fact, already referred to, that cocaine causes profound psychic effects and very readily becomes a drug of addiction with disastrous effects on the addict.

For this reason many attempts have been made, and with considerable success, to find substances which have the locally anæsthetizing properties of cocaine, but are without its dangerous effects on the central nervous system. The main guiding principle in this reasearch has been to synthesize mole-

cules resembling in outline that of cocaine itself, but differing from it in various ways. The changes can be rung in many ways and among the substances which have been synthesized are several which are of proved therapeutic value. Among them may be mentioned stovaine, beta-eucaine, procaine and nupercaine. Of these procaine, which rejoices in the chemical name of *p*-aminobenzoyldiethylethenol hydrochloride, is perhaps the most important.

Despite the availability of such substitutes cocaine is still widely used, particularly by eye surgeons, whose work calls for an absolutely dependable drug. They prefer to use cocaine, the properties and behaviour of which are so well known, rather than to risk new drugs, possibly equally satisfactory, about which less is known. Furthermore, cocaine has the very definite advantage of penetrating particularly readily into the cavity of the eye. It is, however, possible that comparatively soon it may be possible to dispense with cocaine entirely and to rely entirely on the various synthetic substitutes. Such a course would be of great value in checking cocaine addiction for, if no cocaine was required for medical purposes, all traffic in it could be made illegal. At present it is often impossible to distinguish between cocaine ultimately destined to medical practitioners and that which finds its way into the hands of addicts.

Severe cocaine poisoning causes convulsions, unconsciousness and collapse. Death generally results from respiratory failure. Barbitone is a valuable antidote to cocaine poisoning, and it is customary to give an injection of sodium barbitone about an hour before giving any substantial dose of cocaine or any of the substitutes related to it. Mild poisoning is accompanied by pallor, sickness, and dilation of the pupils of the eyes. The pulse is quickened and breathing is irregular. Despite these symptoms, which might be expected to act as a deterrent, the mental stimulation which the drug causes gives it, once tried, a deadly fascination even for the most strong-willed. It is difficult to describe the sensations produced by the drug, particularly as they are to some extent subjective, as, not unexpectedly, few addicts have recorded their experiences. The general effects appear to be a suddenly increased vitality, ability to create in drama, poetry and art, and general exhilara-

tion. Then follows a return to normal, then a melancholy depression and a few nights of insomnia. This is the worst that results from a single venture into cocainism but probably few are content to stop there. If larger quantities are taken the above symptoms are enhanced and exhilaration may verge into delirium. The confirmed addict loses both his mental and his physical health. He becomes pallid and thin, weak-witted and deluded. The only real effort he is capable of making is one directed towards obtaining more of the drug which is killing him. A characteristic feature is lack of moral restraint. He will thieve, even murder, when tormented by his craving. Lack of restraint is particularly evident in sexual relationships. In women it is said that erotic sensibility is increased, which may account for its popularity among prostitutes ; in men it is said that cocaine causes a tendency towards homosexuality.

The symptoms of severe chronic cocainism are perhaps more terrible than those caused by any other drug of addiction. Besides being cursed with physical ill-health addicts suffer the wildest hallucinations. All their senses are deranged. They hear loud noises, music, shots, strange and threatening voices. They see monsters, colours changing as in the revolving of a kaleidoscope, everything is distorted. Their mouths are filled with strange tastes, their noses perceive strange smells. Their skins suffer continual itching and irritation. They imagine themselves to be the victims of persecution, heroes, great personages. Finally they permanently pass out of the realm of sanity and must be confined. Too often, however, they are not put under restraint until they have done injury, sometimes fatal, to themselves, those they once loved, or to innocent strangers.

Cocaine is generally taken by sniffing a little of the white powder, perhaps a tenth or a fifth of a grain, up one nostril. This results in a physical symptom of the confirmed addict. The septum of the nose—the membrane separating the two nostrils—loses its sensitivity and cannot resist bacterial infection. Gradually an abscess starts which ultimately perforates the septum completely.

It has been said that cocaine addiction first started with ill-starred attempts to cure morphinism by substituting cocaine.

This kind of treatment was prescribed in the last decade of the nineteenth century. Whether this story is true or not it is certain that cocainism was well established before the war of 1914–18. One of the first examples reported was in the United States army, where a number of men were found to have obtained the drug from a prostitute. At the same time cocaine, under the name " koko " was being illicitly traded in the great cities of Europe, particularly Paris. The Great War greatly stimulated the evil practice. The peoples of the fighting nations suffered great hardships and naturally turned more readily than in normal times to drugs which would divorce them from their troubles and sorrows, if only for a few hours. This tendency was unfortunately fostered by the fact that great quantities of cocaine found its way into the hands of the public from surplus military supplies. In the years immediately after the war cocaine was sold almost openly in Berlin, then notorious for the viciousness and dissipation of its night-life. Huge profits were made and many were swindled—though doubtless to their benefit—by the sale of spurious white powders which contained little, if any, cocaine. New York and Chicago, too, were centres of cocainism, as indeed were almost all great cities of America and Europe. So serious was the position that the League of Nations was called upon to lend a hand in suppressing the trade, with the result that the prevalence of the vice definitely declined. Indeed the suppression of the trade in this and other narcotics may be reckoned among the most useful achievements of the ill-fated League.

It is greatly to be feared that the appalling conditions existing in Europe after the war just concluded, probably far worse than anything previously experienced in the history of the world, will lead to a big increase in drug addiction of all kinds, among which cocaine is probably the most deadly. There is at the moment, however, no precise information on this point.

CHAPTER ELEVEN

MISCELLANEOUS VEGETABLE DRUGS

PREVIOUS chapters have described at length seven vegetable drugs of outstanding importance and given some account of many more. Nevertheless, these by no means exhaust the list even of those drugs which are familiar to the general reader, far less the much greater number which have some medicinal value and have been described in the scientific literature. The purpose of the present chapter is to give a brief account of some of the more important of those remaining.

The Deadly Nightshade, a tree which grows to a height of six feet and bears cherry-like berries which have an often literally fatal fascination, yields the valuable ophthalmological drug atropine. This substance is an alkaloid, known as a mydriatic alkaloid, which has the power of diluting the pupil of the eye, thus facilitating examination of its internal structure. The Latin name of the tree, *Atropa belladonna*, is singularly apt. Atropos was one of the three Parcae, daughters of Nox and Erebus, whose duty it was to cut the threads of human life —a grim reference to the very poisonous nature of the tree and its fruit. Belladonna means, of course, " beautiful lady," a reference to the use of the juice of the leaves and berries for cosmetic purposes. Women well know the remarkable powers of their eyes in attracting the opposite sex and in former days used belladonna to dilate the pupils to make their eyes even more dark and mysterious than they really were.

Because of the considerable demand for atropine and related drugs the Deadly Nightshade is specially cultivated for medicinal purposes. Because of its danger to children and others the tree is often destroyed in the wild state and is becoming increasingly rare. Atropine as such probably occurs only in traces in the tissues of the tree, whose main alkaloid is known as hyoscyamine. This is an *optically active** substance (cf. quinine, page 42), which in the course of ordinary methods of extraction is converted into the optically inactive, or *racemic*, form known as atropine. The yield is greatest from

* It is actually the laevo isomer.

the leaves, which contain about ½ per cent of pure hyoscyamine; the berries contain rather less.

Atropine is widely used by oculists, but it also finds other applications in medicine. It has been used to relieve the night sweats which are a distressing feature of tuberculosis and to diminish the activity of the salivary and gastric glands. Atropine poisoning is characterized by distension of the pupils of the eye, dryness of the mouth (due to the action on the salivary glands), delirium, and double vision. Acute poisoning results finally in general paralysis, owing to the action of the drug on the involuntary muscles, and finally in unconsciousness and death.

Hyoscyamine was originally so named because it occurs in various species of *Hyoscyamus*, a botanical family to which the common henbane belongs. This plant has been prized for its medicinal virtues for centuries. The seeds were used by the Babylonians three thousand years ago to relieve toothache and in parts of England and in other parts of Europe, particularly the Balkans, it is still so used. The Egyptian Henbane, *Hyoscyamus muticus*, is used commercially for the preparation of hyoscyamine.

Hyoscine is another drug closely related to hyoscyamine and atropine. With morphine it is used to induce " twilight sleep " in childbirth ; it is also commonly used in the manufacture of asthma cigarettes. It occurs in several species of the botanical genus *Solanaceae*, which includes the Deadly Nightshade, the potato and the tomato. It is best obtained commercially, together with hyoscyamine or atropine, from *Datura metel*, a white-flowered plant which is a native of India. There it is said to be used by robbers to overcome their victims. The thornapple (*Datura stramonium*) is a closely related Asiatic plant which also yields hyoscine and hyoscyamine from its leaves and seeds. The Nubians smoked the leaves to relieve asthma and other bronchial complaints ; it was introduced to England by the great herbalist John Gerard, who obtained the seeds from Constantinople.

The root of the mandrake, whose high medical esteem was mentioned in the introductory chapters (page 14) also contains the drug hyoscyamine and hyoscine. It contains also a related drug known as mandragorine. Mandragora was formerly

prized as an aphrodisiac and was a common constituent of love-philtres. Taken with wine mandragora has pain deadening properties and so was used for relieving toothache, for surgical operations, and for similar purposes. It was valued, too, as a soporific and as such as mentioned several times by Shakespeare :

" Not poppy nor mandragora
Nor all the drowsy syrups of this world
Shall ever medicine thee to that sweet sleep."
(Othello).

Few herbs are more closely linked with magical practices and superstition than the mandrake ; some instances of this were quoted in the introductory chapters. Much centred round the frequent resemblance of the mandrake root to the human body. Apart from its use in herbalism the mandrake is often used as a charm. It is sometimes carried by women in Kent as a charm against sterility ; a similar custom prevails in Greece, Turkey and Syria. Mountaineers in the Alps often carry it as a protection against mishap.

Monk's-hood or wolf-bane, of which the common species is *Aconitum napellus*, is another plant whose poisonous properties have been known from earliest times. According to Theophrastus its classical name is derived from Aconae, a town near which it grew abundantly. The leaves, flower-head and root of the plant contain a number of related, highly poisonous alkaloids known collectively as aconitine. Pure crystalline aconitine was first prepared in 1860. It is a drug with an evil reputation and has often been used as a criminal poison. It is referred to as such by a number of classical writers, including Ovid and Virgil. The ancient Gauls are said to have used it as an arrow poison and it is used today for this purpose in parts of Asia. One-fiftieth of a grain of pure aconitine may prove fatal. The symptoms of aconitine poisoning are dilation of the pupils, weak pulse, partial paralysis, dizziness and acute mental fear. In severe poisoning death follows quickly and is generally preceded by almost complete paralysis.

The root of the monk's-hood bears some resemblance to that of horse-radish and a number of accidents have resulted from mistakes in identity. The plot of a murder novel has been made to turn upon this circumstance. The plant grows wild in

many parts of Europe and Asia, and is sometimes grown in gardens for the sake of its flowers. The root and leaves find some applicationin medicine for stimulating the sensory nerve endings of the skin and so producing a sensation of tingling and warmth.

The common hemlock, *Conium maculatum*, is generally identified with the plant used by the Greeks in a method of state execution. Plato has left us a vivid account of the death of Socrates in 402 B.C. after a draught of hemlock. According to this account, in excellent agreement with modern observations, the symptoms of hemlock poisoning are a gradual paralysis, creeping upwards from the feet, followed by convulsions and death. There is no evidence of mental disorders ; Socrates was conscious and coherent almost to the last. The active principle of hemlock is an alkaloid known as coniine, a colourless liquid with an odour reminiscent of mice. The root bark of the pomegranate (*Punica granatum*) contains a series of related alkaloids similar to those of hemlock ; it finds a limited medicinal use as a vermifuge. Hemlock leaf may be prescribed for internal use as a sedative and antispasmodic ; externally it is a soothing application for hæmorrhoids and other irritations of the rectum.

Hellebore is another well-known poisonous plant. The White Hellebore of pharmacy is the dried root of *Veratrum album* ; it contains a number of alkaloids known collectively as veratrine. Similar substances are present in the Green Hellebore, *Veratrum viride*. Veratrine is a powerful poison. Medicinally it is sometimes used for external application for the relief of neuralgic pains. The Black Hellebore, *Helleborus niger*, is a member of a different botanical genus ; it is known also as the Christmas rose. The dried roots of the plant find some use as a purgative. The active principles are glucosides (page 33) known as helleborin and helleborein. Helleborin is a strong purgative ; helleborein is an even stronger purgative and also has a cardiac effect similar to that of digitalis. Helleborein is found also in the Green Hellebore.

Although strychnine finds considerable use in medicine it is more commonly known merely as a poison. It is obtained from the seeds of various species of *Strychnos*. In the pure state strychnine, first isolated in 1819, consists of white crystals with

an intensely bitter taste. For this reason, when given with criminal intent, is it often administered in coffee, which masks its bitterness. Strychnine was not known in Europe until about the seventeenth century, but as it forms a constituent of various arrow poisons used by primitive tribes it can probably claim a long, if not entirely noble, descent. The first use of strychnine is said to have been for poisoning cats and dogs ; today very large quantities are used in all parts of the world for destroying vermin.

Symptoms of strychnine poisoning generally make their appearance very suddenly ; the most characteristic feature is the violent twisting and convulsion due to contractions of the muscles. The muscles of the face are among those affected and their contractions produce a very characteristic grinning expression, similar to those of tetanus, known as *risus sardonicus*. Despite the alarming symptoms produced by large doses, strychnine is of value in medicine as a stimulant of the central nervous system. The general effect is a sharpening of all the senses such as those of touch, smell, and hearing. It also has a specific effect on the conjunctiva of the eye, enlarging the field of vision and making the sight more acute. As a stimulant it is often used as a single full dose in moments of crisis, as in pneumonia. Its continuous administration, except in very tiny quantities, may do more harm than good. Nux vomica also contains the related alkaloid brucine, which is rather less poisonous than strychnine.

Caffeine is another valuable stimulant, though much milder in its action than strychnine. It occurs in a variety of plants which are extensively used for making stimulating beverages such as tea, coffee, cocoa, cola and maté. Pure crystalline caffeine was first isolated, from coffee, in 1821. There is now a considerable demand for it, both for medicinal purposes and for preparing various kinds of beverage, and it is prepared industrially from tea-dust and tea-waste. The last war, however, made apparent the limitations of this source of supply and it has been announced that synthetic caffeine is shortly to be manufactured in the United States. Psychological tests have demonstrated that caffeine stimulates all the psychic functions—a fact which accounts for the world-wide popularity of caffeine-containing drinks. Caffeine is often associated in

plants with the closely related theophylline and theobromine. The former is a diuretic and as such is used medicinally.

The corm or root of the meadow saffron, *Colchicum autumnale*, contains the important alkaloid colchicine, sometimes used in the treatment of gout. Much more important, however, is the recently discovered power of colchicine to affect the number of chromosomes, bearers of the hereditary factors, in living cells. Extensive use has been made of this property both in investigating the mechanism of heredity and for developing new and improved strains of various kinds of plants.

Ephedrine is an alkaloid which was first isolated, in 1887, from the Chinese drug Ma Huang. It is produced by various plants of the genus *Ephedra*. Its chemical structure and physiological effects are similar to those of adrenaline, a hormone produced by the adrenal glands of the body. Like adrenaline it relaxes the bronchi and causes vaso-constriction (page 104). It is, however, much more stable than adrenaline and can, therefore, be administered by mouth. It is very extensively used in the treatment of asthma, for which purpose its stability makes it much more suitable than adrenaline. It is also used medicinally to relieve congestion of the mucous membranes of the nose and throat.

Calabar beans, the fruit of *Physostigma venenosum*, yield the valuable drug physostigmine, of value in ophthalmology. The beans are so poisonous that, before they began to be exported for medicinal purposes, the natives of Calabar and the region round the mouth of the Niger used to destroy the plant wherever they found it. Physostigmine has an effect opposite to that of atropine, causing contraction of the pupil and a lowering of the intraocular pressure. Jaborandi, the leaves of *Pilocarpus Jaborandi*, yields another alkaloid, pilocarpine, whose action on the eye is similar to, though rather milder than, that of physostigmine. Both drugs promote the flow of saliva, decrease the frequency of the heart heat, and increase sweating.

Chaulmoogra oil, expressed from the seeds of *Taraktogenos Kurzii*, has been used for more than half a century in the treatment of leprosy. The active principle is chaulmoogric

acid. A very similar substance, hydnocarpic acid, is obtained from the seeds of *Hydnocarpus anthelmintica.*

The South American arrow poison, curare, long regarded as too deadly a poison to use for medicinal purposes, has been brought under control only within the last few years. It has made up for nearly a century of disrepute by being now welcomed as an almost essential adjunct to modern anæsthetic procedure.

Curare has a remarkable power of paralysing voluntary muscles, but various factors made it impossible to turn this property to practical account. Curare is the crude native arrow poison and is prepared in different ways by different tribes ; many varieties contain plants of the *Strychnos* family and are accordingly rich in the very deadly strychnine and brucine. Curare as such is too variable a substance to use in medicine, but recently a constituent of curare, curarine, has been isolated and found to have most valuable properties. As it is a pure substance the dose can be controlled by weight. The main use of curarine is in abdominal surgery, and a recently published report describes its successful use in one thousand cases. Its great value lies in the fact that it quickly causes profound relaxation of the abdominal muscles with little or no damage to vital organs and without stopping peristalsis (the natural movement of the intestines). Only small amounts of general anæsthesia are necessary to keep the patient asleep and insensitive to pain. The after-effects, due to the anæsthetic, are thus greatly reduced. Curarine is a dangerous drug and its successful use demands experience both of the precise dosage and of the effects of over-dosage. One of the most serious of the latter is the cessation of breathing. It is a remarkable tribute to the recent advances in anæsthetic technique that, as this effect is of brief duration and breathing can easily be restored by artificial respiration, this drawback is not now regarded as a serious one. Curarine can also be used for a variety of other surgical procedures, such as the manipulation of joints, and can in some instances replace cocaine. The hazards of the latter drug have been mentioned in an earlier chapter. The full possibilities of curarine remain to be assessed, but the drug has already been proclaimed a milestone in anæsthesia.

CHAPTER TWELVE

WHAT OF THE FUTURE?

AS previous chapters have dealt very largely with the history and present use of drugs derived from plants it is appropriate that this final chapter should be devoted to consideration of possible future developments.

The introduction of scientific methods gave new life to the work of the early herbalists and physicians and the impetus of this is not yet lost. It became possible to distinguish really useful plants from those whose medicinal virtue was inferred only from fanciful speculation, and to assess the value of newly examined plants by logical methods. By chemical analysis it became possible to isolate, or at least to concentrate, the active principles of many medicinal plants. The introduction of chemical and biological methods of assaying the potency of drugs made their use much safer. Medicine thus gained digitalis, quinine, cocaine and morphine. That the usefulness of examining more and more plants for new drugs is not ended is amply instanced by the very recent discovery of penicillin. The success of penicillin has resulted in an intensive search throughout the world for new antibacterial products of moulds. Already this has led to the discovery of a new substance, streptomycin, which shows promise of clinical use in attacking infections not sensitive to penicillin.

The methods used in assaying the antibacterial potency of mould products have recently been extended to the investigation of flowering plants. In an investigation recently completed at Oxford, carried out in the same laboratory as that which saw the development of penicillin, some 3,000 different species of plants were examined for new antibacterial substances suitable for use in medicine. Similar work has been done, independently, in America. Both teams of research workers found that many different species of plants contained powerful antibacterial substances. A few of these have already been isolated in the pure state and their chemical and physiological properties have been investigated. Although no startling discoveries have yet been made the vast number of different

plant species yet to be examined leaves work for many years to come, from which really important results may well come.

There is unfortunately no single test for medicinal virtue in plants. A test for antibacterial activity, for example, will not reveal the presence of substances having narcotic effects or action on the heart. Earlier chapters have shown how diverse are the effects of plant drugs ; equally diverse are the tests necessary to detect them. Other factors make the search for new plant drugs unavoidably slow. Thus we have already seen in the case of drugs such as hashish and opium that many substances are not distributed uniformly in the tissues of the plant. It is, therefore, necessary to test separately all parts of the plant—flowering-head, stem, root, seeds and leaves. Furthermore, substances may not be present in the plant at all stages in its growth. Plants grown under different climatic conditions show various differences in their chemical constitution.

It is, therefore, evident that the systematic examination of the Plant Kingdom for new drugs is a long and tedious business. Nevertheless, the many notable successes already recorded give ample encouragement for the continuation of the work. It is sometimes believed that the growing use of synthetic drugs, produced empirically and not in imitation of an already known natural drug, will in time make unnecessary the search for new drugs among natural sources. Such a view shows a very limited appreciation of the capacity of modern routine chemical synthesis. It is perhaps true to say that modern chemical resources are such that, given sufficient facilities, most natural substances (except those, such as proteins, which have very large molecules) could in time be synthesized in the laboratory. Nevertheless, there are tens of thousands of natural substances, even relatively simple ones, whose synthesis by existing methods would be of such great difficulty as to be quite impracticable unless there was some very important goal in sight. This is, for example, the case with penicillin. The importance of this substance is such that it has been worth while to devote the time of hundreds of chemists, over a period of years, to the task of synthesis. Though this will undoubtedly be achieved in time it has not been as yet, except on a minute scale. It is, therefore, evident that plants and

other natural sources can provide thousands of substances, of which at least a few can reasonably be expected to be useful, which will not be provided by the chemist for years, possibly centuries, to come. The tedious search for new drugs in plants can thus continue secure in the knowledge that it does not represent work which could be done more quickly and easily in other ways.

The chemist, indeed, very often gains a clue to valuable new drugs from study of a natural one. It is often possible to evolve from one drug, which itself has some dangerous qualities, another in which useful properties are retained or enhanced, and undesirable ones suppressed. A classic example of this is the development of aspirin, probably the most widely used of all drugs. Aspirin is a synthetic drug modelled on the natural drug salicin, derived from the bark of willow and poplar, and long used for the relief of rheumatic and neuralgic pains. Again, the identification of the chemical nature of cocaine guided chemists into the synthesis of a wide range of new drugs, such as procaine and novocaine, possessing local anæsthetic properties. This kind of work will undoubtedly lead to many more equally important results.

Another undoubtedly important field for future research lies in the investigation of the mode of action of drugs and of the relationship between chemical structure and physiological action. Such research will yield results of great academic and practical importance. Understanding of the nature of drug action will point the way to the development of drugs with predictable qualities. At present this kind of work is almost wholly empirical and the only certain method of discovering the physiological effects of any unknown substance is to subject it to biological tests. This sort of research may also suggest the presence of valuable therapeutic properties in substances where they are at present wholly unsuspected. It is relevant to mention that investigation of the natural substance allyl thiourea resulted in the discovery that a related substance, thiouracil, known for many years previously, was a valuable drug for the treatment of Graves' Disease. Undoubtedly the chemist's existing store-house, in which there is already well over half a million different substances, contains many valuable drugs yet to be recognized as such. The powerful synthetic insecticide

gammexane, for example, was known for more than a century before its remarkable properties were realised. Detailed study of the relationship between chemical structure and pharmacological action may lead to further discoveries of equal value. In any such programme the vegetable drugs, so numerous and with such diverse properties, must play an important part.

Yet another important field for future research, and one as yet almost unexplored, is the study of the way in which drugs are formed in plants and the function they fulfil in the economy of the plants in which they are found. It is a remarkable fact that, for almost every one of the numerous vegetable drugs in use today, there is no convincing explanation of their presence in the plant. The importance of quinine to the cinchona tree or of morphine to the poppy, for example, are complete mysteries. It is possible that some of the poisonous or obnoxious substances are a form of protection against grazing animals or the ravages of destructive insects and other pests. It is possible, too, that some drugs result from the combination of waste products formed in the vital processes of the plant, and represent a method of inactivating substances which might otherwise be harmful. Yet such explanations have little to commend them except plausibility; the factual evidence is scanty indeed. Information on these points is valuable, not only for its own sake, but also because any added understanding of the metabolic processes of plants may prove of great importance in solving outstanding agricultural problems. In this respect it may be mentioned that the remarkable new weed-killer, Methoxone, was developed as a result of studies of growth-promoting substances first discovered, in minute quantities, in living plants.

For many drugs there is a large, and often increasing, demand, and there is an urgent need for finding improved sources of them. An important form of research, therefore, concerns itself with the investigation of various strains of drug-producing plants in the hope of finding new and high-yielding varieties. Sometimes such varieties can be found growing wild and can be adapted for cultivation. An alternative method, and one finding increasing favour, is to develop new strains by systematic breeding. As an example of what can be done in this way it may be remarked that strains of

Penicillium notatum now being used for the commercial production of penicillin produce several times as much as those used in the early days of research. Such work is, of course, of particular interest to those whose livelihood is dependent on the production of natural drugs. While it is by no means true that the mere fact of being able to synthesize a drug means that it can compete economically with the natural product, this possibility is always present. It is, therefore, of vital interest to the grower to make every acre of plantation give the highest possible yield, particularly when the margin between the cost of the natural product and that of the synthetic is a small one.

The study of drugs is often of unexpected value in the botanical classification of plants. In earlier chapters it has been pointed out that plants belonging to the same botanical family often produce substances possessing a general chemical resemblance. The *Solanaceae*, for example, a family which contains such diverse plants as the potato, tomato, and deadly nightshade, produce drugs of the atropine type. Similarity in their chemical constituents has sometimes revealed botanical relationships which are not immediately apparent from purely morphological studies. Introduction of chemical methods into botanical classification will certainly be profitably pursued in the future.

It is thus apparent that the study of vegetable drugs, although one of the most ancient branches of science, still has a great future before it. Not only can it be expected to lead to new drugs as important as any described in the earlier chapters of this book, but it can also make important contributions to allied fields of science, notably botany and chemistry.